ANNUAL REVIEW OF PHYSIOLOGY

EDITORIAL COMMITTEE

J. P. BAUMBERGER
J. FIELD
H. D. GREEN
V. E. HALL
H. W. MAGOUN
G. K. MOE

Responsible for organization of Volume 19
(Editorial Committee, 1955)

J. P. BAUMBERGER
H. D. GREEN
V. E. HALL
H. W. MAGOUN
G. K. MOE
J. P. QUIGLEY

ANNUAL REVIEW OF PHYSIOLOGY

VICTOR E. HALL, *Editor*
University of California at Los Angeles

FREDERICK A. FUHRMAN, *Associate Editor*
Stanford University

ARTHUR C. GIESE, *Associate Editor*
Stanford University

VOLUME 19

1957

PUBLISHED BY
ANNUAL REVIEWS, INC.
AND THE
AMERICAN PHYSIOLOGICAL SOCIETY

ON SALE BY
ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U.S.A.

LIBRARY
UNIVERSITY OF CALIFORNIA
DAVIS

ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U.S.A.

FOREIGN AGENCIES

The Maruzen Company, Limited
6 Tori-Nichome, Nihonbashi
Tokyo

PRINTED AND BOUND IN THE UNITED STATES OF AMERICA
BY THE GEORGE BANTA COMPANY, INC.

PREFACE

Physiologists outside of the Soviet Union have long been poorly informed of the work of their colleagues within that vast area. The growing demand for a means of making knowledge of their contributions readily available provides the basis of a plan to include in various Reviews published by Annual Reviews, Inc. chapters on current science in the U.S.S.R. as described in the Russian language periodicals. The project, as supported by the National Science Foundation, calls for the preparation of these special chapters by scientists who have the necessary competence for the task.

We have decided to divide the whole of physiology into several parts which will be reviewed successively, each review spanning about five years. The obvious choice for the first of these reviews was the field of neurophysiology. For the writing of this review we were fortunate enough to obtain the services of Dr. W. T. Liberson, who, as a native of Kiev, possesses the necessary linguistic competence and as a neurologist has the equally necessary grasp of the subject matter. We are confident that our readers will turn to this chapter with curiosity if not with deeper interest, and find there answers to many questions concerning this field, doubtless the flower of Russisn physiology.

The second such chapter will deal with the physiology of the cardiovascular and allied systems, and will be prepared by Dr. E. Simonson. The third will be devoted to metabolism and endocrinology, with Dr. H. Leicester as the author.

We regret that circumstances made it impossible for Dr. W. F. H. M. Mommaerts to complete his promised review on the Physical Properties of Protoplasm. Illness has prevented Dr. E. C. Black from preparing his chapter on the Comparative Physiology of Transport Pigments. These losses have been in part offset by the inclusion of the second part of the review on Physiological Effects of Radiation by Drs. E. P. Cronkite and V. P. Bond.

We wish again to make public avowal of our genuine indebtedness to the authors who have given so generously of their life blood in the preparation of this volume. Were it not for the almost unanimous claim of previous authors to have markedly profited from the task, we would never have had the courage to solicit their cooperation in accomplishing these labors. Even Hercules never attempted a chapter for an Annual Review. Credit is also due to our Editorial Assistant, Mrs. Tove Hunchar, and to her co-workers in the Editorial Office for their loyal assistance, and to our printer, the George Banta Company, Inc. for their indispensable cooperation.

J.P.B. H.D.G.
J.F. V.E.H.
F.A.F. H.W.M.
A.C.G. G.K.M.

TOPICS AND AUTHORS
ANNUAL REVIEW OF PHYSIOLOGY
VOLUME 20

PREFATORY CHAPTER, *W. J. V. Osterhout*
PROTOPLASM: MITOCHONDRIA, *O. Lindberg and L. Ernster*
GROWTH: HORMONAL REGULATION, *A. E. Wilhelmi and J. Russell*
MUSCLE, *S. Gelfan*
KIDNEY, WATER AND ELECTROLYTE METABOLISM, *W. D. Lotspeich*
RESPIRATORY SYSTEM, *A. B. Otis*
DIGESTIVE SYSTEM, *K. J. Öbrink*
BLOOD: FORMED ELEMENTS, *M. H. Jacobs*
PHARMACOLOGICAL ASPECTS OF PERIPHERAL CIRCULATION, *D. Bovet*
HEART, *V. Lorber*
CONDUCTION AND TRANSMISSION IN THE NERVOUS SYSTEM, *W. D. M. Paton*
SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM, *V. Mountcastle*
VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM, *H. D. Patton*
HIGHER FUNCTIONS OF THE NERVOUS SYSTEM, *R. Masland*
VISION, *G. S. Brindley*
ADENOHYPOPHYSIS AND ADRENAL CORTEX, *G. Sayers*
REPRODUCTION, *T. Mann and C. Lutwak-Mann*
COMPARATIVE PHYSIOLOGY: TEMPERATURE AND ACCLIMATIZATION, *F. E. J. Fry*
COMPARATIVE PHYSIOLOGY: EXCRETION, *A. W. Martin*
SKIN, *W. B. Shelley*
RUSSIAN PHYSIOLOGY: CARDIOVASCULAR ASPECTS, *E. Simonson*

CONTENTS

	PAGE
PREFATORY CHAPTER (THE INCREASING RESPONSIBILITY OF THE PHYSIOLOGICAL SCIENCES), *G. Liljestrand*	1
TRANSPORT THROUGH BIOLOGICAL MEMBRANES, *E. J. Harris*	13
DEVELOPMENTAL PHYSIOLOGY, *L. G. Barth*	41
PHYSIOLOGICAL ASPECTS OF HEAT AND COLD, *J. Bělehrádek*	59
PHYSIOLOGICAL ASPECTS OF HYPOTHERMIA, *C. Kayser*	83
TISSUE METABOLISM (PHARMACOLOGICAL ASPECTS), *M. B. Chenoweth and G. L. Ellman*	121
RESPIRATORY SYSTEM, *H. Bjurstedt*	151
DIGESTIVE SYSTEM, *S. Mellinkoff*	175
BLOOD CLOTTING, *F. D. Mann*	205
BLOOD VOLUME AND ITS REGULATION, *E. Brown, J. Hopper, Jr., and R. Wennesland*	231
PERIPHERAL CIRCULATION, *L. H. Peterson*	255
EFFECTS OF RADIATION ON MAMMALS, *V. P. Bond and E. P. Cronkite*	299
COMPARATIVE PHYSIOLOGY: OSMOTIC AND IONIC REGULATION IN AQUATIC ANIMALS, *L. C. Beadle*	329
HEART, *M. B. Visscher and G. J. Stephens*	359
VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM, *P. D. MacLean*	397
HEARING, *I. Tasaki*	417
PITUITARY AND ADRENAL GLANDS, *B. T. Donovan and G. W. Harris*	439
REPRODUCTION, *C. H. Sawyer and B. V. Critchlow*	467
SOMATIC ASPECTS OF THE NERVOUS SYSTEM, *W. R. Adey*	489
KIDNEY, *S. E. Bradley*	513
RECENT ADVANCES IN RUSSIAN NEUROPHYSIOLOGY, *W. T. Liberson*	557

Annual Reviews, Inc. and the Editors of its publications assume no responsibility for the statements expressed by the contributors to this *Review*.

G. LILJESTRAND

THE INCREASING RESPONSIBILITY OF THE PHYSIOLOGICAL SCIENCES

By G. Liljestrand

Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden

The enormous impact of scientific research on practically every phase of human life has long been known and emphasized. It is obvious, however, that the understanding of science and its inherent possibilities for good and for evil has increased very much in the mind of the general public in the 20th century, and especially during the last four decades. Undoubtedly the experiences from the two World Wars have had a decisive influence on this development. Nobody can have failed to observe that a nation's prospects of defending itself have been intimately connected with its scientific standard and its ability to apply the results of scientific research. Chemistry and physics have here been in the foreground—witness such achievements as modern explosives, radar, loran, the rocket weapon, and of course, above all, the atomic bomb. But medical research has also contributed much of high value—one might call attention to chemical warfare and the means of combating it, the achievements of chemotherapy against malaria and numerous other infectious diseases, the studies on wound shock, the impressive development of air medicine, etc. It is significant that in all these cases experimental medicine, or physiology in its widest sense, has been deeply engaged.

With good reason it has been said that the transition from the earlier modes of warfare to that of today, where science becomes applied to destruction on a wholesale basis, "marks . . . a turning point in the broad history of civilization" (1). It is tragic that two World Wars should have been necessary to convince people everywhere of the fantastic potentialities of science; but it would have been still worse if this knowledge had been monopolized for military purposes. The practical demonstration of the fact that numerous important problems could be solved quickly enough if sufficient means were provided made a deep impression. Moreover, many of the new discoveries could be applied immediately to peace conditions. The result has been a general realization that science, more than anything else, can contribute to a better utilization of the earth's resources, can bring people together by improved communications, combat disease as never before and considerably increase the active span of life. In other words it is now realized that science is able rapidly to raise our material standard. In fact, the position of science in modern societies has entered a new phase.

A natural consequence of the altered situation is that the official attitude towards research has changed considerably in many countries. At the beginning of the century most university departments had great difficulties in obtaining adequate personnel and financial support for research work; teaching was their main task. Only few institutions had been founded for research alone, e.g., in the United States the Rockefeller Institute for Med-

ical Research (1904) and in Germany the Kaiser Wilhelm Institutes for Biochemistry, for Experimental Therapeutics, and for Brain Research (1911). In 1913 an important step was taken in Great Britain when the Medical Research Council was founded with ample means at its disposal. The situation today is very different in many countries. Numerous new university or pure research departments have arisen, and it has even sometimes been difficult to find sufficiently trained people to take care of them; their staffs have grown considerably and financial support has increased in a way that would formerly have seemed impossible. Medical Research Councils have been established in many places, fellowships created and so on. The following quotation from 1950 (2) gives an idea of the enormous increase in the financial resources for medical research in the United States:

> During the past twenty years . . . the annual contributions by foundations to medical and allied research amounted to approximately ten million dollars, while, for some years prior to World War II the contribution by the federal government to research in the field of medicine had ranged from four to five million dollars annually. With the onset of the war, however, the federal government , through such agencies as the Atomic Energy Commission, the United States Public Health Service, the Children's Bureau , and the armed services, broadened the scope of its interest and greatly increased the amount of its contributions. Federal expenditure for research in medicine and in the basic medical sciences in 1947 amounted to twenty-eight million dollars, nearly three times the sum available from philanthropic foundations. An increasing fraction of federal funds has been devoted to an expanding grant-in-aid program in support of research being conducted at the universities. The great expansion of federal support for medical research did not terminate with the cessation of hostilities, on the contrary, it has become one of the central pillars of an emerging new philosophy of government—the assumption of direct responsibility for the health and welfare of the people. The report of the President's Scientific Research Board, published in 1947, strongly recommends a progressive increase in federal government expenditures during the next ten years, to reach a goal of over two hundred million dollars annually by 1957, a sum more than twenty times the total now available in these fields from the private foundations.

To this should be added the very considerable amounts used for research by different nutritional and pharmaceutical firms.

Other countries, less wealthy than the United States, have of course not been able to increase their support for medical research on a scale at all comparable to that described above. But in many of them a very gratifying improvement of the situation has taken place. It may without exaggeration be said that a revolution has taken place as regards the economic and personal conditions for medical research. This gives hope for continued progress against illness and suffering, but at the same time it imposes a heavy burden of responsibility on the shoulders of the representatives of research. Many important questions must be settled if results are to correspond to the expectations one is entitled to have.

It is only natural that definite practical problems may be especially

favoured by the money-providing authorities, first and foremost during war conditions but to some extent also in peace time, and that relatively large sums may be allotted for such purposes. It is also understandable that a donor who is interested in some particular illness, perhaps through the loss of some near relative or friend, will desire to support investigations on that disease. In the long run, however, the prospects of attaining valuable results are undoubtedly more favourable if at the same time the basic sciences as a whole are encouraged. When the frontier to the unknown is moved forward, entirely new, often undreamed of possibilities may arise. One is tempted to repeat this well-known fact when one observes the disproportion between the very large amounts at the disposal of cancer research and the relatively modest results obtained. Langmuir has given a beautiful illustration of the unpredictable results of research in his own case (3). After four or five years of rather free academic work in the laboratory of General Electric Company on heat transfer in air and in various gases he was able to obtain results of real importance to industrial research that could not have been reached by a direct attack on the problem. He states that in the United States alone the public was saving nightly over one million dollars in power in consequence of this research. Medical research offers numerous examples of a similar nature. Two of the best known are Richet's discovery of anaphylaxis, which opened a new and fascinating field of research, and Fleming's discovery of penicillin with its well-known practical consequences.

It is true that "no single factor is as important as the men responsible for a research undertaking" (4). But the freedom to choose their own problems is essential to most scientists, and "medical research is often handicapped if it is pressed to be immediately applicable" (5).

The fundamental rôle that must be attributed to the physiological sciences also for the solution of many clinical problems makes a fruitful cooperation between the theoretical and the practical branches of medicine imperative. There are two main ways of accomplishing this. The future clinician himself may make such acquaintance with experimental medicine as will enable him to use its methods at the bedside. Great progress in different branches of clinical medicine have resulted from such endeavours. One might here refer to the rapid development of our knowledge and treatment of diseases of the heart and blood vessels that has followed to a great extent from the application of methods long known in physiology. Similar situations exist in many other fields, e.g., with regard to diseases of the respiratory organs and the kidneys, where the modern development of physiology has enabled a deepening of the analysis, and also to neurology, where the study of action potentials, once confined to the university departments of physiology, has become a vary valuable tool. Unfortunately, it is frequently impossible for the clinician to find time both for extensive activity as a physician and for research work with the often very refined techniques that have been elaborated in the physiological departments. Here it seems necessary to obtain "full-time professorships" in the clinics. At present only very few posts of this kind exist in

most countries. It is, however, an urgent desideratum that more be created. Not only would this advance scientific progress, but the results would certainly be of great benefit to the patients.

Another way of combining the theoretical and the practical, and one that has given good results, is to attach well-trained physiologists to the hospitals, where they not only supervise routine work in the clinical laboratories but also, and chiefly, engage in research work both on indications from their medical colleagues and in following initiatives of their own. Such departments already exist in many hospitals, but there is great need for more of them.

The free exchange of results and ideas emanating from scientific work in all parts of the world is extremely important. Unfortunately, this is sometimes prevented altogether or rendered very difficult. Thus for economic or military reasons, for instance, many new achievements are kept secret, and this applies to the physiological sciences as well as in numerous other fields. It is of course understandable that a firm that has spent large sums of money to find a new remedy should be unwilling to part with the results obtained unless it can be sure of suitable compensation. And it is also obvious that increased knowledge of, say, man's reactions to the great forces at play in the modern aeroplane and of how to increase his ability to withstand the stresses to which he is exposed in this connection may give a certain superiority to the nation in possession of the new facts if this knowledge is kept secret. But it cannot be denied that a free exchange in the cases adduced as well as in many others might be invaluable from a more general point of view. The lesser the secrecy, the better the opportunities of applying the results in different directions for mankind as a whole.

But even if the results are made available, it may often be difficult to learn about them. The usual way of making new findings known is, of course, to publish them in the scientific literature. Theoretically this gives everybody access to them, but practically it is far from the case. The number of scientific publications is overwhelming. In his opening address at the International Physiological Congress in Boston in 1929 Krogh (6) calculated that papers referring to physiological problems had increased from about 3,500–4,000 a year in 1904–1907 to 11,500 in 1920 and about 20,000 in 1927. It is probable that a further rise has taken place since then, though it is difficult to decide which papers should be included—the Section Physiology, Biochemistry, and Pharmacology of *Excerpta Medica* with its 5,788 numbers for 1955 is certainly far from complete. The enormous number of scientific publications greatly enhances the difficulties. Every scientist must feel that he can only follow the literature in a very limited field. Through the abstracting journals and review articles he will get a general idea of what is going on. The older literature is to a great extent forgotten, including numerous papers that have definitely been of great importance. This is regrettable, since the latter have considerable educational and inspirational value; the historical perspective is thus also lost. It is to be hoped that the monographs planned by the

American Physiological Society will help to counteract the tendency to forget the work of our predecessors. The days of the great handbooks of physiology as a whole are probably gone, but it seems possible that such works or monographs covering the most active fields will replace them and be better adapted to modern needs.

In their own special fields of research, however, scientists will not be content with the general survey mentioned. They will feel the necessity of reading the pertinent papers *in extenso* or at least their summaries, and of being able to do so as soon as possible after publication. The Current List of Medical Publications is a most valuable modern addition to our resources, and enables one to take cognizance of the titles of articles that have recently appeared. But here one is confronted with the real difficulty. Some hundreds of years ago practically every new scientific achievement was published in Latin and thus made internationally known. In our time, however, no common scientific language exists. French, German and English have in turn been the foremost medium, though none of them has gained a monopoly. It seems very doubtful that in the future any of them should become accepted throughout the world as the only one to be used for scientific publications. Furthermore, many other languages are playing a greater rôle each year as media for original publications; and there is reason to believe that the rapid rise and development of scientific work throughout the world, even in countries which have hitherto hardly taken active part in research, will lead to the more widespread use of these languages. There are signs, however, that the need for better contact through scientific literature is being keenly felt in different countries. Thus the starting of *Acta physiologica latino-americana* is motivated in the following words (7): "As long as the surprising ignorance of Latin languages persists in those countries in which scientific activity is most developed, it will be necessary to publish the more important papers (from South America) in the language of those countries, or to add a summary in English and in another language widely understood in the scientific world." On the other hand, some medical periodicals have appended to every article a summary in "Interlingua," that "can be read by at least 95 per cent of those who are technically qualified to read the same text in a version in French, or in Spanish or in German or in English" (8). This is a revival of the old notion of using Esperanto as a means of communication between scientists, an idea strongly advocated by Ostwald (9). Possibly Interlingua has certain advantages, and its use may well prove valuable, but the arrangement does not strike at the root of the evil. The problem of translating a paper from one to another of the occidental languages is usually fairly easy, but quite other obstacles are encountered when it is a matter of becoming acquainted with a paper written in a language differing fundamentally from those already mentioned. There is a great and important scientific literature in Russian, Polish, Czechoslovakian, Japanese, etc. which is now more or less a closed book for most physiologists in the United States or Europe. Some time ago the Russian physiological journals gave short summaries in one of

the western languages, but unfortunately this was discontinued about six years ago, obviously for political reasons. It is to be hoped that something will be done to improve the situation. This is certainly in the interest of all concerned. Nobody likes his work to remain unread or neglected, and our colleagues in all parts of the world are certainly anxious to influence through their work the development of our common science. A year ago I had the opportunity of attending, on invitation, the eighth Russian Congress for Phsyiology, Biochemistry, and Pharmacology in Kiev. I spoke to several colleagues there about the desirability of having their work made more generally accessible. They usually agreed on this point, though some seemed to entertain the notion that we ought to learn Russian, a somewhat unrealistic idea. In one or two quarters the conviction was expressed that measures will soon be taken to facilitate the exchange of ideas. Since then the first number of *Review of Czechoslovak Medicine* has appeared to "fulfill a natural and earnest desire of all Czechoslovak medical scientists to bring their work before a truly international audience" (10). It will "systematically review all noteworthy developments in Czechoslovak medical research by means of full translations of original work as well as annotations and reviews." This is indeed a step in the right direction, and one must hope that this praiseworthy example will be followed in several other countries. There is, moreover, certainly room for cooperation also in other directions. Thus one might ask: is it necessary to duplicate or even triplicate the large abstracting service? At present we have not only the old *Berichte über die gesamte Physiologie* but also the corresponding sections in Excerpta medica and in the *Soviet Medical Reference Review* (in Russian). Could not this waste of energy be avoided? The questions touched upon here are of course, of the greatest importance not only for physiology or medicine as a whole, but for all sciences. These problems ought to be seriously discussed by our Union of Physiological Sciences and then by ICSU or UNESCO.

Interest in the new development of research work is not restricted to the scientists themselves. The lay public, too, is anxious to learn about it. Since the expenses are mainly paid by the people as a whole, it is natural and not unimportant that they should to a certain extent be kept informed. It seems desirable that scientists should contribute here with "readable but not sensationalized accounts of science in our society" (11). Many physiologists have taken an active part in such work. I need only mention such names as those of Barcroft, Cannon, Carlson, Hill, and Krogh.

The importance of personal contacts between scientists is well-known to all those who have been engaged in research work, though it varies a good deal according to temperament. On the whole, those belonging to Ostwald's classical type (12) are probably less inclined than the "romanticists" to discuss their subjects orally with their colleagues, the slow reaction in the former case being sometimes disadvantageous. One may guess that some would even be in sympathy with the well-known American physiologist who refused a friendly invitation to discuss a paper before its publication with

the words: "I believe in polemics." Usually, however, a scientist will find it not only stimulating to talk personally with others who have been working on similar problems, but he will also derive great personal satisfaction from such meetings. This was emphasized by Berzelius during his visit to England (1812) in a letter to a friend in Sweden (13): "It is difficult to describe the pleasure a scientist enjoys in the company of ten to twelve others who are as keenly interested in the same science, but surely it cannot be interchanged with anything else." And a little later he mentions his first meeting with Davy in the following terms: "We made experiments, we disputed, we ate and drank and at last went to the Opera where Davy had a box."

Even apart from the very real value of exchanging ideas with experienced specialists in one's own field of research and the personal satisfaction to be derived; a visit to a foreign country will afford many other advantages, as pointed out by Linnaeus in his medical lectures, where he says (14): "He is happy who may stay at home all his life, in the atmosphere to which he is used, and is spared from roving. But he will not thereby become more intelligent, he may instead become capricious and inhuman, and believe that only those who have lived in his native place are decent fellows. He thinks everything of himself and pays no attention to remonstrances. The noble knowledge of himself, his own nothingness, his ignorance and want of experience he considers of no value or as folly. The best means of eradicating this self-conceit is travelling, where such people might learn to adapt themselves and become well-bred after having seen other manners, having conversed with many and become agreeable when they have got rid of their roughness."

There are certainly few better ways of increasing understanding between nations than frequent visits between their people.

The best way for a physiologist to establish personal contacts is undoubtedly by working for some time—not too short—in a foreign laboratory. He will then be able to devote his time wholly to research, without being disturbed by the numerous factors to be considered at home; he will learn about new methods and lines of thought, and will acquire something of the special spiritual atmosphere of the laboratory. If the same spirit reigns there as was once so highly praised in Carl Ludwig's laboratory, he will also have opportunities of following other investigations being carried on in the institute. Time spent in a foreign laboratory is thus often both happy and fruitful. Not infrequently it leaves impressions of decisive importance for future activities, and at the same time it affords rich opportunities of establishing ties of friendship. Even if working under such fortunate conditions falls chiefly to the lot of younger scientists, it is certainly very useful also later on in life to be able to work in a foreign laboratory. The sabbatical year affords such opportunities, but unfortunately it is still only a beautiful dream in most countries.

Though the prospects of obtaining financial aid during a stay at a foreign institute have improved greatly and such visits have been multiplied during the last decades, they must be supplemented by short meetings with col-

leagues at intervals. In this respect the international physiological congresses have had an extremely important function. I well remember the deep impression I received from the first of these congresses that I attended. It was in Groningen 1913. At the opening ceremony eloquent speeches were given by Starling on Mosso, and by Tigerstedt on Bohr which immediately created a feeling of direct connection to classical physiology. We could see demonstrations and hear men like Abel, Einthoven, Haldane, Hamburger, Krogh, Pavlov, and Zuntz. I had started some work on the physiology of respiration and after some hesitation I took the liberty of asking Krogh about the possibility of working for some time with him. The result was that I became his first pupil from abroad at the zoophysiological laboratory in Copenhagen. Thus the contact established during the congress had the greatest importance for my future. With the rapid increase in the number of participants at the congresses contacts have become more difficult to establish. It has even been maintained that like the giant saurians of an earlier geological period the international physiological congresses have grown too large to be able to survive. In their stead, symposia in which groups of specialists meet for a few days either in combination with the congresses or independently of these have been favoured.

The symposia have certainly proved their value, especially when they have been carefully prepared, so that the participants have been able to study introductory reports beforehand, and thus been enabled without waste of time to get thoroughly into the subjects to be discussed. I have less confidence in those symposia at which, and without any special preparation, people make their remarks on the basis of their general knowledge. Nor does it seem necessary to publish every passing fancy that is mentioned in the course of the discussion. The literature is already too voluminous, and it is sometimes trying to have to read a detailed report on such a discussion before arriving at the principal point. As a rule the number of participants at the symposia is rather limited. It is natural that only such workers are invited as have for some time been actively engaged in research in the field under discussion. But many young scientists who would be greatly interested in taking part in the symposium are kept out. I recall a small occurrence at the Congress in Groningen which has a bearing on this point. At the final meeting the place for the next congress was discussed. Finland and France had both extended invitations. A speech by the American physiologist S. J. Meltzer was decisive. When he pointed out that Paris would be better located than Helsingfors for the younger physiologists, for whom the congresses had the greatest importance, the first mentioned place was chosen. It should not be forgotten that the congresses are still stimulating for the workers of the future in our science; they, too, should have this opportunity of presenting their own results and of having them discussed. It has become necessary, however, to ensure that the congresses do not become too large and thereby too expensive and too difficult to handle. Two different courses seem to be open. One is the arranging of regional meetings. These have often

been tried and found useful. Thus we have special physiological congresses in the United States (with the Federation), in Germany, in the French-speaking countries, in Scandinavia, in Russia, and so on. The drawback here, of course, is that the really international character of the congress is lost. The other solution of the difficulty is to keep the congresses at the international level while limiting the scope to some part of physiology, e.g. cardiology, neurophysiology, endocrinology. The withdrawal of the biochemists from the physiology group to start a union of their own is a step in this direction; it will probably be followed by others. The restriction to a narrower field will have the advantage of making possible the inclusion of not only normal but also pathological physiology and, to some extent, medicine. This seems to be a valuable arrangement and a means of stimulating a desirable cooperation with the clinicians.

The fundamental rôle of physiology for expanding medical research makes it an important duty to find and train sufficient numbers of men and women who shall be capable of carrying the torch of ascertainable knowledge further into the unknown. There are urgent demands for research workers for other sciences as well, so competition will be keen, and it will not be easy to satisfy all claims. It ought not, however, to be difficult to enlist the interest of able students for the fascinating study of vital processes—"the best sport in the world," to use Starling's words at the International Physiological Congress in Stockholm in 1926—provided that appreciation of the physiologist's work is accompanied by satisfactory economic remuneration. Otherwise, the younger generation will be forced to take up other occupations despite the attractiveness of physiology. But what are the qualities to be required in the young aspirant if our expectations are to be fulfilled? There is of course no definite answer. Sometimes one's predictions turn out quite well, but often enough one fails in one direction or the other. I would like in this connection to quote the beautiful speech that Pavlov at the age of 87 years delivered to the students of his country. In the English translation by Kupalov it runs as follows (15):

> What can I wish to the youth of my country who devote themselves to science?
>
> Firstly, gradualness. About this most important condition of fruitful scientific work I never can speak without emotion. Gradualness, gradualness and gradualness. From the very beginning of your work school yourselves to severe gradualness in the accumulation of knowledge.
>
> Learn the ABC of science before you try to ascend to its summit. Never begin the subsequent without mastering the preceding. Never attempt to screen an insufficiency of knowledge even by the most audacious surmise and hypothesis. Howsoever this soap bubble will rejoice your eyes by its play, it inevitably will burst and you will have nothing but shame.
>
> School yourselves by demureness and patience. Learn to inure yourselves to drudgery in science. Learn, compare, collect the facts.
>
> Perfect as is the wing of a bird, it never could raise the bird up without resting on air. Facts are the air of a scientist. Without them you never can fly. Without them your "theories" are vain efforts.

But learning, experimenting, observing, try not to stay on the surface of the facts. Do not become an archivist of facts. Try to penetrate to the secret of their occurrence, persistently search for the laws which govern them.

Secondly, modesty. Never think that you already know all. However highly you are appraised, always have the courage to say to yourself—I am ignorant.

Do not allow haughtiness to take you in possession. Due to that you will be obstinate where it is necessary to agree, you will refuse useful advice and friendly help, you will lose the standard of objectiveness.

Thirdly, passion. Remember that science demands from a man all his life. If you had two lives that would be not enough for you. Be passionate in your work and your searchings."

The rules set down by the great physiologist do not, however, apply only to the future scientific workers in Russia, but equally to other groups of citizens, e.g., administrators, engineers, teachers, and so on in all countries. The gradual approach, the appreciation of facts as a solid basis for discussion, patient perseverance, and modesty as well as passion or enthusiasm for the work itself are of the highest value everywhere in human life. The same qualities that we find desirable in the ordinary citizen also seem to be very important for the scientist. One point which Pavlov has not mentioned, and which is also relevant both for the scientist and for others is independent and unbiased assessment of the value and importance of old and new observations and of the validity of the conclusions inferred from them. A moderate distrust of authorities, even the greatest, may sometimes be a useful asset. Independence may also be shown in the choice of new problems. It is possible that this did not appeal very much to Pavlov—we know from Babkin's biography (16) that "only in exceptional cases did Pavlov admit a new worker who wished to carry on independent research on his own problems." He preferred to allot to the research visitor a subject which was the continuation of some earlier work in the laboratory and was thus part of a larger program outlined by Pavlov. This frequently used method may have certain advantages for the teacher and may be valuable for the collection of a large material in a field where the laboratory is especially competent, but I doubt whether it is the best way of stimulating young workers in the long run. It is, of course, a convenient way for a student to become acquainted with some useful technique and to be fairly certain that there will be some tangible result in the end from his work. But he will rarely have the feeling that this is his own spiritual property, and he will hardly have met and conquered the difficulties that will normally arise if he is doing work of his own. Therefore he should not continue too long with projects inspired by others. I have always found it a good sign if a student approaches me with his own ideas, and have considered it my duty to encourage him if the problem seemed worth trying at all. It is interesting to note that in his young days Krogh (17) "had visions of leaders of physiology who could see clearly problems to be studied and the ways of approaching them, and who might distribute them and their separate parts among the laboratories and the

individual workers." Later on he became convinced that such plans cannot and ought not to be realized. "Individual freedom is our chief asset, the mainspring of the really new ideas, the guarantee of progress," he writes. Indeed, independence of general judgment and scientific initiative constitute an essential part of originality, a quality rightly considered to be especially valuable in the research worker.

These considerations bring us to the question of the training of the future physiologist. The natural way is undoubtedly a sufficient period of apprenticeship under a good teacher. Collaboration with another student may be very valuable, leading to stimulating discussions at every step to be taken. Of course it may also be useful to take part in team-work, that modern form. of concentrated group effort which has led to the solution of so many difficult problems. For the reasons given above I do not think that this kind of work ought to dominate; individual achievement should be encouraged. The high specialization of physiological technique makes it desirable, however, that the training in a good laboratory should be supplemented by preliminary studies in chemistry, physics, and mathematics and also by special courses covering important departments within physiology. Such courses have recently been started at the Rockefeller Institute (18) and also in some other places. They are badly needed, and will help to foster a new generation well prepared to take over the study of vital phenomena. It will have numerous opportunities of verifying the words of the Swedish chemist Scheele more than 180 years ago (19): "There is no delight like that which springs from a discovery; it is a joy that gladdens the heart."

The author is well aware that the above remarks contain nothing new or original. They deal with problems which every teacher in physiology will meet in his work and which should be discussed at intervals. Their importance has grown with the increasing responsibility of physiology as a basis for the medical sciences. It is hoped that this will be a sufficient excuse for touching lightly upon them again.

LITERATURE CITED

1. Bush, V., in *Scientists against time*, VII-IX (J. P. Baxter 3rd, Ed., Little, Brown and Co., Boston, Mass., 473 pp., 1946)
2. *Twentieth Anniversary Review of the Josiah Macy, Jr. Foundation*, 21–22 (New York, N. Y., 111 pp., 1950)
3. Langmuir, I., *Lilly Research Laboratories Dedication*, 7–13 (Indianapolis, Ind., 128 pp., 1934)
4. Gregg, A., *The furtherance of medical research*, 76 (Yale University Press, New Haven, Conn., 131 pp., 1941)
5. Gregg, A., *The furtherance of medical research*, 6 (Yale University Press, New Haven, Conn., 131 pp., 1941)
6. Krogh, A., *Am. J. Physiol.*, **90**, 243–251 (1929)
7. Houssay, B. A., *Acta Physiol. Latinoamer.*, **1**, 1 (1950)
8. Editorial in *Circulation Research*, **4**, 1 (1956)

9. Ostwald, W., *Die Forderung des Tages*, 437–512 (Akad. Verlagsgesellschaft, Leipzig, Germany, 604 pp., 1911)
10. *Rev. Czechoslovak Med.*, **1**, 1 (1955)
11. Editorial, *Science*, **123**, 565 (1956)
12. Ostwald, W., *Grosse Männer*, 371–388 (Akad. Verlagsgesellschaft, Leipzig, Germany, 424 pp., 1910)
13. Berzelius, J. J., *Kgl. Svenska Vetenskapsakad. Årsbok*, 325–362 (Almqvist & Wiksell, Stockholm, 372 pp., 1955)
14. *Carl Linnaeus' Skrifter i urval* (K. Hagberg, Ed., 195 Natur och Kultur, Stockholm, Sweden, 283 pp., 1955)
15. Babkin, B. P., *Pavlov, A biography*, 110 (The University of Chicago Press, Chicago, Ill., 365 pp., 1949)
16. Babkin, B. P., *Pavlov, A biography*, 71 (The University of Chicago Press, Chicago, Ill., 365 pp., 1949)
17. Krogh, A., *Am. J. Physiol.*, **90**, 243–251 (1929)
18. Hagberg, K., *Science*, **123**, 216 (1956)
19. Scheele, C. W., *Efterlemnade bref och anteckningar*, utgifna av A. E. Nordenskiöld, 151 (Norstedt & Söner, Stockholm, Sweden, 490 pp., 1892)

TRANSPORT THROUGH BIOLOGICAL MEMBRANES[1,2]

By E. J. Harris

Department of Biophysics, University College, London, England

Symposia on subjects related to transport through membranes provide a wealth of review articles and new facts (1 to 5). Frequent reference will be made to specific articles in these publications. Books dealing with special or general topics in the field include: Davson (6), LeFèvre (7), Harris (8), and Johnson, Eyring & Polissar (9).

In the following discussion examples have been drawn mainly from most recent work without reference back to the originator of particular methods or theories.

Interpretation of Results; Mechanism

Complications in tracer measurements.—In the last article of this series Wilde (10) stressed that applications of isotopes to transport studies were beset with pitfalls, notably those arising from the tacit assumption that rapid mixing occurs within cellular systems. It was simplest to suppose that in a two compartment system the rate of passive transport from a given side would be proportional to the electrochemical activity of the substance on that side. When the fluxes in opposed directions were not proportional to the respective electrochemical activities this was explained by invoking the operation of a chemically mediated "pump," giving rise to a component of flux which is called the "active" part. Chemical mediation may also occur in movements down the gradient. When movement from side 1 to side 2 involves several steps in series, or side 2 has really several compartments, or the material is held on side 2 on a series of adsorption sites then tracer experiments give a complex result capable of taking several interpretations. For example, if the tracer moves as far as an outer adsorption site of side 2 it may then be unable to penetrate further because there is no vacant place ahead of it. The rate of uptake by side 2 will be rapid so long as the outer places are being filled, and then becomes slow. The limit is ultimately set by the internal turnover within side 2. This system can simulate a multi-compartment structure by exhibiting "fast" and "slow" components of exchange.

A special, but most important, case of movement being constrained to take place by a series of displacements along a file has been described by Hodgkin & Keynes (11). Movement of tracer K through the membrane of the squid axon is not proportional to the K flux measured without distinction

[1] This review covers the period from July, 1954 to May, 1956.

[2] The following abbreviations are used in this chapter: DNP (dinitrophenol); P.D. (potential difference); R.P. (resting potential); ATP (adenosine triphosphoric acid).

of tracer. Instead the relation: tracer flux in/tracer flux out = (K influx/K efflux)^n holds, with n about 3. The value of "n" may be the number of places in the file connecting inside with outside. Here then the tracer flux varies as the nth power of the electrochemical activity. This comes about because transfer from one side to the other requires n events each giving one unit of movement in the desired direction. There can be many collisions leading to entry of an ion into the first place of a file, which are followed by others causing its expulsion on the same side. These abortive attempts of the tracer to move to the other side all represent units of flux in one or other direction, since for an ion entering one end of the file another is expelled at the far end. The component of electrical conductivity due to the ion is determined by the effect of changed potential difference on the net movement of charge. Here it will not matter that the ions discharged into side 2 are not identical with those striking the surface on side 1. Hence the conductance depends on true flux, not on tracer flux.

In any system in which movements take place in a serial way instead of being without mutual interference, similar conditions apply. There are suggestions that the interior of muscle (and medullated nerve?) cells comprises an assembly of fixed charges on which ions, mainly K, are adsorbed (12, 13). Either the cell membrane, or the cell interior, or both, may be an interpenetrating network of ion exchanger groups and aqueous phase of the kind discussed, e.g., by Scatchard (14). While the kinetics of site-to-site movement have received attention (15), this was not in relation to tracer movements.

Site-to-site movement of tracer will be strongly influenced by any net stream which is present. The tracer can make little progress against a contrary stream; it is constantly swept out of the material. This may account for the apparent failure of the K of several tissues to be fully exchangeable with tracer [muscle (16), nerve (17), and kidney if anaerobic or at 0° (18)]. All that would be required is that during the exposure to the tracer a small net leak of potassium should set in. The greater the number of sites involved in the movement, the less the rate of leak necessary to prevent further exchange. Support for this proposal is lent by the fact that conditions under which there is no net loss, e.g., raised external K concentration, do lead to full exchange (16, 17). Isolated rat diaphragm, which maintains a constant K content after an initial rapid loss, shows full exchange of its K (19, 20).

No evidence has been adduced that Na movement takes place in a manner similar to that of K (11). Na moves by a different mechanism or to a different place. There are however many examples of cells or tissues having depots of Na of unequal exchange rates; relatively inexchangeable fractions have been described [kidney (18), erythrocytes (21), and muscle (23, 24)]. The inexchangeable Na of frog muscle is also the least easily extracted by water; it is concentrated at the ends of the muscle, pointing to its location in connective tissue (23).

Carey & Conway (24) have discussed the location of muscle Na, much

of which becomes replaced by a mobile K fraction if the tissue is put in high-K media. After various arguments they now (22) favour the localization of 80 per cent of the non-extracellular Na in the sarcolemma.

It is a source of difficulty that complex tracer-content versus time curves, as described by Carey & Conway (24) for muscle K, and as seen also in erythrocyte and kidney ion exchange processes, may result from movements going on either in series or in parallel. Evaluation of a flux may be rendered difficult or impossible; one is thrown back on chemical measurements made with systems in which the component in question is omitted on one side. Although attention has been focussed on the alkali ions there is no reason why the long pore effect should not arise in other cases [Harris & Edwards (25)]. If water moves along narrow pores it would be possible to explain the discrepancy between the rates of diffusion of deuterium-labelled water and of osmosis under equal gradients of water activity. A similar difference is found with frog skin and some egg membranes (26). Tracer movement is slower than osmosis. In a steady state with a DOH for H_2O exchange in progress one can imagine the tracer oscillating between the solution on one side and the first place in a pore instead of crossing to the other side.

Mechanism of ion movement and accumulation.—Little has been elucidated about the chemistry of processes responsible for ion movements. Most examples show that the rate of the metabolically mediated component is saturable; there is a formal resemblance to an adsorption isotherm and to the Michaelis-Menten enzyme kinetics equation. If the carrier groups appear at the surface infrequently compared with the collision rate of the ion the penetration rate will be limited by this factor and saturability does not necessarily imply presence of an adsorbed layer. If carriage inwards from an adsorbed layer is sufficiently rapid an adsorbed layer of ions may never reach the surface-saturation concentration; here the rate will remain linearly dependent upon concentration.

Maintenance of low Na in rat diaphragm is found under conditions where glycogen deposition occurs (27); deoxycorticosterone is unfavourable to both glycogen formation and K retention (28). DNP causes both K loss and fall of organic phosphates (29). In mitochondria the accumulation of K is qualitatively associated with high content of phosphoenolpyruvate (30). These observations show that ion movement against the gradient is associated with metabolism. That the retention of K ions by a cell demands a continuous energy supply has been questioned [Ling (12)]. Shaw & Simon (13) suppose that K of frog muscle is held on sites whose existence depends on continued metabolism. Failure leads to loss of sites and K; restarting metabolism resynthesises sites which can then pick up K.

The selective adsorption of K in tissues is attributed to its smaller hydrated ionic radius. There is no evidence for different degrees of dissociation of K and Na salts of various phosphoric acids [Snell (31)]. The long pore effect already mentioned may provide an alternative way for bringing

about excretion of Na. If one has a specific inward K carrying process which continuously feeds the cell interior with K ions these could entrain Na ions when they subsequently diffuse outwards.

The mechanism of absorption of some substances by yeast has been studied by Rothstein (5, 32, 33). Yeast will adsorb about 1 mM/kg. of uni- or divalent ions. The latter are more strongly held. Addition of Mg will, for example, displace K from the surface. This action does not however affect the rate of K accumulation which shows that here active absorption is not related to adsorption; different loci may be involved. It is interesting that uptake of divalent ions only takes place during metabolism, and then there is a 1:1 correspondence between divalent ion uptake and phosphate absorption.

The uptake of ions by plant roots has received considerable attention. Lundegårdh (34) has reviewed the subject; he considers that anions are carried through the protoplasm on a chain of cytochrome molecules. Alternating changes of valency of the iron cause the anions to move to maintain electroneutrality. Cation movement takes place after an adsorption on the acid groups of the surface. While Lundegårdh considers that inward movement of cations takes place along a line of adsorption sites, without intervention of metabolism, other authors suppose that the cations are carried by a metabolically produced intermediate [e.g., Scott-Russell (35); Epstein (36), (37)]. The dependence of uptake rate on external concentration, as well as mutual interferences between similar elements, can be interpreted in terms of different strengths of adsorption on the surface (36) though it has been pointed out (35) that the subsequent rate of inward transport also varies from ion to ion. One has to think in terms of two processes operating in series.

Uptake of water by plant roots depends on metabolism; it is poisoned by azide (38) or dinitro-cresol which also reduce respiration (39). Whether the movement is a combination of electro-osmosis and osmosis, or an active process, has still to be decided. Movement of some nonelectrolytes, particularly the sugars, into cells and through the wall of the intestine seems to involve temporary formation of a compound which mediates transport through the membrane. The rate of transport by such a system, which requires enzymes at both surfaces, has been compared with that of a cytoplasmic transport mechanism (40). The latter would require faster diffusion through the cell walls than has been observed in free solution and it would demand an excessive energy supply if it operated in the kidney tubule cells (41).

A carrier operating in a membrane can give rise to different kinetics according to whether the carrier is saturated at either or both surfaces. When unsaturated, the kinetics resemble that of diffusion, while with bilateral saturation the rate varies as the difference between the reciprocals of the concentrations. There have been a number of discussions of the possibilities, often with reference to sugars crossing the erythrocyte membrane (40, 42 to 46). Glucose is generally preferentially transported and shows saturation

characteristics while the ketoses are but slightly associated with the carrier. The order of rate of penetration depends on the concentration of the sugars (46). There is evidence that the two sides of the membrane show unequal dissociation constants of the carrier-sugar complex (45).

The nature of the combination involved in sugar transport is unknown. Entry of glucose into rat diaphragm, with glycogen deposition, takes place in bicarbonate but not in phosphate media. Glucose-1-phosphate as substrate only leads to glycogen formation if phosphate is present [Beloff-Chain *et al.* (47)]. Evidently glucose does not move in as ordinary phosphate. Hexoses show specific differences in passing through the guinea-pig placenta, glucose passing easier than fructose [Karvonen & Räihä (48)]. Passage of glucose and fructose through the sheep placenta has been measured. There is a placental formation of fructose in this species (49, 50).

Potential difference (P.D.) and permeability.—The most comprehensive study of the permeability of a membrane in relation to the potential difference across it has been that of Hodgkin & Huxley [(51) for short review; (52) for discussion and earlier references]. They studied the giant axon of the squid by electrical means. Their observations are not therefore disturbed by the long pore effect. The ability to undergo changes of permeability as a result of excitation must be related to a change in structure of the membrane. This change may either be steric or electrical; the latter might be a result of freeing fixed charges. Nachmansohn & Wilson (53, 54) have proposed that upon excitation a bound form of acetylcholine is liberated. This induces a change in the structural elements of the membrane; at the same time the free ester becomes hydrolysed by the local enzyme.

Transient changes of permeability associated with excitation in nerve and muscle are not related to the resting permeability. Hodgkin & Keynes (55) found that dinitrophenol poisons resting Na output but does not inhibit the extra turnover which follows activity. Other treatments remove the capability to transmit an action potential without changing resting ion movements [e.g. salt-free sucrose on squid axon (55); yohimbine on muscle (56)]. That the inward movement of K into the axon is mainly a chemically mediated process has been shown by its inhibition by dinitrophenol, which also leads to a breakdown of the phosphate esters (57). This does not change the resting potential, which shows the action is not merely a consequence of P.D. change on permeability. Grundfest (58) has pointed out that the same resting potential can be measured using Ag/AgCl electrodes as with salt-filled microelectrodes. Hence the chloride ion concentration ratio is not a Donnan distribution between inside and outside for which Cl-reversible electrodes should show zero P.D.

To define the conditions under which ions move, knowledge of the potential differences in the system are essential. In favourable cases (giant axons, frog skin) both sides of the membrane are accessible and the potential difference can be controlled. When the P.D. is made zero by feeding in a suitable current the electrochemical potentials become equal to the chemical

potentials; the respective fluxes of a given ion in opposed senses in a passive system should be proportional to the activities, and between equal concentrations there should be no net movement. When net movement is found between equal electrochemical potentials it is evidence of a chemical process being operative. By this test inward Na movement through frog skin and Cl transfer across the gastric mucosa are active chemically mediated processes. Kirschner (59) and Linderholm (60) find that inward Na movement through frog skin has two components, a passive concentration-dependent part, and an active part. The latter can be related to the outside concentration by an equation like the adsorption isotherm, but influx passes through a maximum not predicted by the theory. Outward movement of Na is passive. It is reduced in amount by encounters between Na ions drifting out and unoccupied carrier groups; hence leakage is less when the carriers are not all occupied by Na ions, i.e., with lower external Na concentrations.

In the gastric mucosa the active Cl movement from nutrient to secretory side has been shown under conditions of zero P.D. [Hogben (61, 62)]. The current is carried by H and Cl ions. There is a considerable backflow of Cl. This does not seem to be a result of free ions because it does not contribute as much to the electrical conductance as expected for passive movement.

A corresponding problem is encountered in the Na turnover of muscle. The Na flux is comparable with the K flux, yet it contributes little to conductance. One may explain this either (a) by supposing that Na moves both inwards and outwards in a combined state; or (b) by supposing that much of the Na movement, takes place between adsorbed material and solution instead of involving passage through the membrane. Conway's depot in the sarcolemma may well behave in this latter manner, but one may ask where the high Na of a muscle which has been K-depleted in K-free solution is accommodated. In this connection it is worth recalling that storage does give rise to a slow moving fraction of tracer Na which is absent from fresh specimens (63).

Linkage of Na and K Movements.—There are an increasing number of cases in which movement of Na is partially dependent upon the K concentration. Presence of K assists Na movement through frog skin [Huf (64)]; this may be related to the maintenance of normal ion balance by the skin cells, for these show exchanges (not in fixed equivalence) between the two ions if external K is reduced.

Harris (65) has discussed Na and K movements in the human erythrocyte and proposed that for each K moved in actively, two Na ions are moved out; in addition there are passive components. In a study of effects of poisons and K concentration on Na flux from the squid axon, though Na efflux depends on K concentration, Hodgkin & Keynes (55) concluded that if Na and K movements are coupled it is not a fixed ratio.

Membranes.—There is now considerable activity in the exploration of the properties of artificial membranes [see (5) which was available only in proof]; these are made with a high density of fixed charges by incorporating

an ion-exchanger resin. The P.D. between solutions separated by a membrane is made up of three components: two "Donnan" potentials arising between respective sides and the solutions, and the diffusion potential across the membrane. The calculation of the P.D. has been discussed at length by Teorell (66) who gives solutions of the diffusion equation for mixed univalent electrolytes. A general solution has been provided by Schlögl (67).

Hitchcock (5, 68, 69) has demonstrated that the Donnan potential between colloid and crystalloid solutions exists in the absence of the separating membrane; it is a consequence of the slow diffusion of the colloid. Overbeek (70) pointed out that departure from ideal behaviour of colloid systems may be greater at low concentrations than at high ones; in high concentrations the local fields round the colloid overlap enough to average out large differences.

Potential differences across, and ion movements through, charged membranes are discussed by: Scatchard (5, 14, 71), Sollner (5, 72) and Sollner, *et al.* (73, 74). The passage of an external current, as well as the spontaneous diffusion of ions through these membranes can give rise to considerable electro-osmosis.

Using a "Neptonic" resin, Juda, Marinsky & Rosenberg (75) found 300 cc. water moved per Faraday. The electro-osmosis has been measured for a number of membranes and ions by Sollner (72) who favours an explanation based on pores of different sizes, such that some have only counter ions (charge opposite to that of the fixed charges) present in the fluid and others have both counter and co-ions (charge equal to that of fixed charges) present, giving rise to a local circuit. Schlögl (5, 76) has adduced an explanation depending on differences of hydrostatic pressure and electric field between the ends of a single pore. The direction of the water movement is determined by the relative mobilities of counter and co-ions.

So-called rectification by membranes, i.e., their possession of a non-linear current-P.D. characteristic, can be related to the ease of entry of mobile ions into the charged material. Since the counter ion concentration is equal to the sum of fixed charges and co-ion concentration, the conductance is determined by the extent of co-ion entry. When this is favoured by the applied field acting in the sense high-concentration-to-membrane material conductance will be high (67). Irreversible thermodynamic methods have been applied to the discussion of permeability [Kirkwood (5, 77); von Bertalanffy (78)].

Application of optical and electron microscopy to biological membranes reveals an increasing complexity. It seems that some membranes have two distinct layers with a space between [lobster axon: Tobias & Bryant (79); nerve: Robertson (80, 81), Geren (82); kidney cells and mitochondria: (237)].

Frog skin has been shown to possess a basement membrane which is the seat of the P.D. (83).

Microinjection.—Transport studies on ions leaving cells are facilitated if labelled ions can be introduced directly into the cells, for this avoids having

a highly exchanged outer layer such as immersion in tracer solution is apt to produce. Introduction of ions into the interior also permits study of the membrane P.D. as function of the internal composition.

Falk & Gerard (84) injected KCl and NaCl into frog muscle with little effect on the resting potential, one-third of which they ascribe to the operation of the Na pump. Grundfest *et al.* (85, 86), and Hodgkin & Keynes (87) found that addition of K ions to the inside of the squid axon had little effect on R.P. According to the former authors the R.P. fell only when conduction was blocked; this needed about 40 μg. of K. Addition of Na was more effective (8 μg. needed to block), while divalent cations were still more potent (less than 1 μg). Hodgkin & Keynes report little effect from Mg, while Ca liquefies the axoplasm and causes block. Tobias & Bryant (79) introduced ions into the lobster giant axon. They also applied the ultramicroscope to a study of the internal structure; the interior is filled with a gel traversed with liquid-filled channels running axially. Particles within the axoplasm are free to move in the liquid, but some are held immobile in the gel.

Particular Cells and Tissues

Muscle.—Exchange studies made on isolated muscles meet the difficulty that the permeation is delayed by the time taken for ions to diffuse through the extracellular spaces (or to move through the outer fibres towards the inner ones). K exchange in the rat diaphragm is slowed on this account [Creese (19)]. While the K of the diaphragm will all exchange (at 37°) only half the K of cat muscle will exchange (at 20°) [McLennan (16)] unless the external K concentration is raised. K efflux from the rat diaphragm is reduced by raised Ca concentration [Gossweiler *et al.* (88)]. K entry into chronically denervated muscle is slower than into a control (89).

Extraction of loaded frog muscle with water shows that the degree of equilibration of its K with tracer is not uniform (23). As the first part of the K liberated has the highest specific activity, the appearance of a fast fraction in kinetic studies may be accountable. When the quantities of radioactive K liberated are divided by a diminishing specific activity to convert them to quantities of "chemical" K the initial curvature of the time curve is reduced or abolished.

Johnson (90) has compared the time courses of the loss of labelled Na, SO_4, and sucrose from frog sartorii. The fast fractions of all three correspond to an extracellular space in excess of the widely quoted 13 per cent. The reviewer has recently measured inulin and sucrose spaces in sartorii and found results between 15 and 30 per cent. The space varies widely from specimen to specimen. In Johnson's experiments both SO_4 and sucrose showed slow moving fractions. The substances are unlikely to have entered the cells and it is suggested that the slow fraction is from material either trapped in the vascular system or held between adherent fibres.

Steinbach followed net movements of Na from Na-rich muscles when these are placed in media with (say) 10 mM K (91, 92). If one calculates the

rate constant for Na efflux from the data it is similar to values found in comparable media for tracer Na output. Net Na gain from K-free media however is slower than expected from the tracer Na output rates in these solutions.

The change in gross ion composition of muscle during growth has been followed by analysis and extracellular space determination. The increasing K and decreasing Na content is attributable to a diminishing extracellular space (93).

The internal pH of muscle has received attention. It has been argued that the Donnan distribution holds but this is now discounted. Caldwell (94) by direct measurement of the pH of crab muscle fibres found that the interior was only about 0.6 unit more acid than the exterior. Hill (95) used as an indicator the fact that lactic acid production in muscle ceases if the interior is more acid than pH 6.3. He found that some acid formation will take place even with external pH 4.5. The cell must keep itself less acid than corresponds to a passive distribution of H ions. The only agent that leads to a rapid acidification is CO_2.

Crab myoplasm has been analysed (96). Both Na and Ca are present, showing that these elements do occur within the cell and are not wholly on the surface. Total ions in crab muscle are lower than in the exterior, and there is an anion deficiency. Reduction of external osmoles causes swelling of the muscles (97). The ratios of internal to external concentration of Cl and Na remain about 1/10, but that of K increases from 10/1 to 20/1.

Isolated frog muscles maintain low Cl and Na in natural media (blood, plasma) better than in saline mixtures (24). The Na output from heart muscle is increased by tension (98). The movement of K into certain hearts is slowed by corticosteroids; as these have less effect on the rate of output there is a net K loss (99, 100). The effect of strophanthin (on a frog sartorius) is to increase K loss to K-free solution in the resting state, but loss during stimulation is unaffected. It even reduces loss during stimulation in DNP (101). Digitoxin slows uptake of phosphate by heart and causes breakdown of the phosphate esters (102).

An increased rate of net loss of K to K-free solution can either be a result of depolarisation, which increases efflux by removing the electrical constraint, or of an increased permeability. The latter, unlike the former, will also lead to an increased influx if K ions are added to the external medium. So in physiological conditions with K ions present a cell will maintain a constant level of K if the basic permeability is altered but will lose K if it is depolarised. It is valuable to know if a given agent tested on K output also changes K uptake and resting potential. It has been reported that cardiac glycosides and cholinergic drugs increase the net K loss from cardiac muscle but not from mitochondria, while other agents induce K loss from both materials (103). It is likely that the K permeability of the heart tissue is increased; this is indicated by electrical studies. In experiments where skeletal muscle is treated with acetylcholine (104) the K loss may be ascribed to a depolarisation spreading from the end-plates.

Study of the movement of K between smooth muscle (taenia coli) and the surroundings shows that activity of the tissue is associated with increased K outflow; any agent (histamine, acetylcholine) which increases tension, or stretching, increases the output. Epinephrine increases the rate of uptake (105).

Of the sugars, normally only glucose penetrates muscle readily. Other sugars possessing the same configuration of the groups α and β to the aldehydic group will penetrate mammalian muscle under the influence of insulin or as a result of stimulation (106 to 111). Sugar absorption is inhibited by epinephrin (112). Since DNP also inhibits, this seems to be associated with the supression of the part of the hexokinase activity (10 per cent) associated with particulate material (113).

Erythrocytes.—The Na and K exchanges of the erythrocyte are more complex than was originally thought. Human cell Na includes a part (2 m.eq./l.) which exchanges in a few minutes and which, for this reason, is removed if the cells are washed before measurement of tracer content. The main fraction of the Na (10 m.eq./l.) exchanges with a rate constant about $0.3hr^{-1}$, and a smaller part exchanges at about one per cent of this rate (21, 114).

K exchange can be expressed in terms of the sum of a fast fraction (four per cent of the total K) and a major slow fraction (115).

Ion movements are discussed in terms of there being passive, concentration-dependent fluxes, with additional active chemically potentiated fluxes moving against the electrochemical potential gradients (65, 116, 118). K influx, for example, rises sharply as the external concentration is raised from zero to a few millimoles, but more slowly as concentration is further increased. This latter increase is attributed to the passive, concentration-dependent part of the influx. Rate constants for passive movement in and out presumably only differ by a small factor arising from the Donnan asymmetry (65); for some cells this is found to be true (116, 118). Tosteson & Robertson (117) find however that K movements in duck cells cannot be fitted in this way. Comparisons have been made of rate constants holding in the discoid and sickled forms of cells from sickle cell anaemia (119, 120, 121). While it is agreed that sickling increases rates of passive movement (of Na, K and Cs), perhaps by unblocking pores, there is disagreement on whether active movement is the same (121) or increased (119). Sickling probably changes the surface/volume ratio. It increases the amount of the readily exchanged Na fraction (121).

Studies have appeared concerning the red cells of the tortoise (122, 123), chicken (114, 122), duck (117), pigeon (124), and some mammals (118). Amongst the nucleated cells K uptake requires respiration in chicken and tortoise but uptake by duck cells is faster anaerobically (116, 117). Influx is increased by fluoride but reduced by iodoacetate. Tortoise cells require Ca ions if they are to keep a low inward permeability to Na; in the absence of

this ion (unless replaced by Co or Mn) they gain Na and water (123). Active movements of Na and K in rat cells are slowed by deoxycorticosterone (125).

Further doubt has been cast on the importance of the acetylcholine-cholinesterase system in red cells [see Wilde (10)]. Adding an enzyme inhibitor to a non-metabolising suspension does not increase K loss [Goodman *et al.* (126)].

The action of fluoride on human cells has been reported to depend on the concentration applied (Eckel, 127). Intermediate concentrations (30 m*M*) cause faster K loss than Na gain. Iodoacetate poisoning has been studied [Love *et al.* (128)]. Poisoning human cells with lead causes a loss of K; this takes place as if two different groups of cells or two fractions of K of unequal mobility were present (129, 130). Partition between the fractions is pH sensitive. Complexing agents such as ethylene diamine tetra acetic acid (EDTA) remove part of the effect of the Pb (130). The Pb is held in a fairly labile state for it exchanges at a rate similar to the rate of loss of the K. It has further been found that heavy metal poisoning may cause an increased inward permeability to K (131). This resembles an effect of 30 m*M* fluoride (127).

Exposure of erythrocytes to visible or ultraviolet light in a NaCl medium leads to an increased rate of K against Na exchange without affecting the glycolysis. There may be some oxidation of constituents of the cell membrane (132).

The permeability of erythrocytes to anions has been compared between species and between anions. The rate of replacement of cell Cl by sulphate in some cells depends on the square of the difference: final concentration of SO_4 in cells—concentration at the time in question. This can be explained by assuming that a large diffusion potential is set up when the cells are mixed with the anion solution. The rate of anion movement then depends both on concentration gradient and P.D., that is on the electrochemical potential difference (133, 134). Uptake of phosphate can be accelerated by ATP and inhibited by Ca or Mg ions. This may be the reflection of the effect which ATP has on the solubility product of magnesium phosphate (136). Phosphate adsorption was related to external concentration by the Freundlich isotherm by Jonas (137) who considers that there is formation on the cell surface of a complex of phosphate, calcium, lecithin, and protein. Phosphate enters the cells from the adsorbed layer. Glycine penetrates turtle cells faster in the absence of O_2, though O_2 is needed for its incorportion into protein (139). Work on sugar permeability has already been mentioned; sugar entry into foetal erythrocytes shows the same characteristics as into cells from adults. The cells from foetal sheep have more K than cells from the adults (138). It has been observed that cortisone reduces fructose permeability (135).

The cells containing the respiratory pigment of *Phascolosoma* behave in

a way similar to erythrocytes when tonicity changes are made. Their permeability to water and some nonelectrolytes has been measured (Love, 140). Values are lower than for ox cells.

Leucocytes.—The behaviour of leucocytes resembles that of high K erythrocytes. The cells lose K on cooling and regain it on incubation with glucose. Net rates as high as 100 m.eq. K per hr. per kg. cell water are seen. Cell Na is 67.5 m.eq./kg. water and K 105 m.eq./kg. water (Hempling, 141).

Medullated nerve.—The question of the effects of the nerve sheath on ion penetration has been resolved. The sheath delays ion movements into the intact nerve (142, 143). It hinders loss of excitability on exposure to CO_2 (144). Shanes (145) has measured the rate of penetration of the isolated sheath, by making it into a bag. Na emerges with a time course described by two exponentials. This is ascribed to the Na coming from the sheath itself, and that part which comes from the interior of the bag, passing through the sheath. The slow component has a time constant of two to three hr. Comparison of ion emergence rates from intact and desheathed nerves shows that desheathed nerve exchanges Na faster than intact nerve. The time course of movement from the desheathed nerve can be described by adding two exponentials; this is true of supposedly nonpenetrating substances (SO_4, sucrose) as well as Na (146). The slower component, like that found in muscle for the same substances, might derive from a space where the fluid is occluded by lipide. In nerve this could be the water associated with the myelin.

The space required to accommodate Na, SO_4, Cl and sucrose at the externally applied concentration has been measured for toad nerve [Shanes & Berman (147)] and the Na and inulin spaces for cat nerve [Krnjević (148)]. There is more Na than corresponds to filling the extracellular space estimated from sucrose or inulin. While part of the excess Na is shown by the kinetic results to be slower moving, and probably intracellular, there is more of the mobile fraction than would fill the space. The conclusion is that Na is adsorbed on material present extracellularly. As in toad nerve the sucrose space (49 per cent) is less than the Cl or SO_4 space (61 per cent) the anions too may be subject to adsorption; alternatively part of the extracellular water is confined in a relatively impermeable place (the myelin?) which sucrose cannot enter.

It is important to note that movement of the slow fraction of the Na is sufficiently rapid compared with the loss of the fast, extracellular, fraction to cause mutual interference (143). Extrapolated fast and slow fractions do not therefore correspond in amount to extracellular and intracellular amounts. Both groups (143, 146) have discussed the question of whether the ions only pass through the area of the node or through the myelin sheath in addition. If only the node were involved in ion movement it would have to be several hundred times more permeable than membrances bounding other excitable tissues. If one accepts that ion movement in the resting

state takes place over the whole area this does not imply that the shifts during activity are similarly spread.

The toad nerve will show net changes of K content if put in K-free and K-containing solution. It gains some Na which is not lost again in Ringer's solution (142); the rate constant applying to Na turnover is the same whether or no the net gain has occurred (146). An increased permeability to Na and K in Ca-free solution is inferred from potential measurements on the nerve of *Leptodactylus ocellatus* (149).

When a length of nerve is exposed to Ringer's there is a loss of K and gain of Na at the cut ends, for these are partly depolarised. The middle part of the nerve also can be shown to be losing K to the solution by analysing the latter. The amount of K per unit length in the middle of the nerve sample is held steady by a migration of K along the axis [van Harreveld & Russell (150)].

K influx and Na efflux from rabbit nerve are diminished by cooling, whereas K efflux is accelerated (17). The K of this tissue, like some muscles, does not all equilibrate with tracer.

The haemolymph of insects sometimes has a high K concentration. The nervous system is surrounded with a sheath which can shield it temporarily from the haemolymph (151). The muscles are rather slowly penetrated by K ions on account of the connective tissue present.

Incorporation of phosphate into frog nerve depends on metabolism; it is inhibited by cooling, and by azide, and also by increased Ca concentration. The latter limits phosphate ion concentration (152). Movements of Na, K, and Br into Pacinian corpuscles have been measured (Gray & Sato, 153). The ionic conductances of ganglia have been measured (154).

Non-medullated nerve.—The ion movements through the membrane of the giant nerve axon of *Sepia* and *Loligo* have been studied extensively by Hodgkin & Keynes (11). When the nerve is poisoned, K movement is passive. In the poisoned nerve the P.D. at which influx and efflux become equal agrees with that calculated from the relation $E = kT/e \ln K_i/K_e$. The anomalies in tracer studies, presumably arising from the presence of long pores, have been mentioned. An additional demonstration of the interference between inward and outward movements of K ions is the reduction of efflux which an increased external K concentration brings about under conditions of constant P.D.

K fluxes were measured across a short length of membrane under conditions of controlled P.D. The P.D. could be set either by current flow from an external source, or by changing polarisation of adjacent lengths of the axon by altering external K (11). That the maintained current flow out of a nerve when it is kept depolarized is all carried by K ions was shown by Hodgkin & Huxley (155).

Active movements of Na and K which take place through the axon membrane are of K inwards and Na outwards (11). There are in addition passive

components of the fluxes which remain after poisoning and which increase if the concentration is raised. The active Na efflux requires presence of K ions in the external medium; it is unaffected by 10 mv. change of resting potential. Na efflux to choline solution is slightly more than to sea water, while to dextrose solution it is slightly less than to sea water. Tracer Na injected into the nerve is excreted at a steady rate within one minute of its introduction (87).

Yeast.—Adsorption on yeast has been mentioned. The cell seems to have two compartments, the outer may be a space between two membranes or the volume of thick membrane. While the outer volume is readily equilibrated with most ions and substances the inner volume is only penetrated by certain of these under conditions of metabolism. Phosphate and divalent ions enter during metabolism; the divalent ion is a 1:1 proportion with phosphate ((Rothstein 5, 32, 33). Pyruvic acid will penetrate the resting cell, but the ion is only absorbed during metabolism (Foulkes 156).

Yeast absorbs K from concentrations exceeding 5×10^{-5} *M*. It is striking that metabolism increases the rate of loss to concentrations below this level. This suggests that loss takes place rather as a result of dissociation of a K-carrier complex than by a leak. Leakage is minimum at pH 4.5; the increase in acid might be indicative of an H for K exchange in the carrier during its exposure to the outer medium (32). Normally yeast will accumulate K in exchange for H, but if K is omitted from the medium other cations will enter; a Na yeast has been prepared (Conway & Moore, 157). This yeast pumps its Na out in exchange for K when the latter ion is presented (158). Conway argues that the exchange is not coupled because K influx is stopped by azide without affecting the Na output to water. Azide added to Na yeast in KCl also reduces Na output to the value found in water, which may represent K-independent movement. The intervention of a redox system in bringing about ion movements in yeast is supported by the fact that the addition of dyes of different redox potential change the rates of ion movement. Increased potential increases K absorption and H excretion rates. On the other hand the rate of Na excretion from Na-rich yeast is diminished (159). Addition of desoxycorticosterone slows Na extrusion in KCl but not in water (160).

Sugar does not diffuse into the yeast cell (32). Entry can be poisoned with uranyl ions and then the rate depends on sugar concentration according to an adsorption isotherm curve. Addition of O_2 permits sugar uptake even in presence of uranyl ions. The relative conversion of sugar to alcohol and to CO_2 can be changed by variation of external K concentrations (161). This may be due to changes in activity of surface enzymes induced by K, for K does stimulate hexokinase. Other effects common to hexokinase activity and fermentation are inhibition by UO_2 and Ca, and reversal of inhibition by Mg.

Frog skin.—Sodium moves inwards from epithelium to corium through frog skin as a result of both active and passive processes. Poisoning the for-

mer with dinitrophenol leaves the latter operative. In this condition the ratio: influx/efflux corresponds to the electrochemical concentration ratio [Schoffeniels (162)]. External acidity below pH 6 reduces the active movement and increases the passive permeability. The active movement is still more affected by reducing the pH of the solution on the inner side; below pH 8 both active movement and passive permeability diminish (163). These findings are interpreted as meaning that the active process involves an H for Na exchange. The dependence of Na fluxes on Na concentration has been studied by Linderholm (60), and Kirschner (59). Although efflux and net efflux can be fitted by an adsorption isotherm to the Na concentration, there is a maximum influx from 40 m.eq./l. which remains unexplained (59). The Na influx from solutions having Na in excess of 30 m*M* is increased by atropine, histamine and curarine (164).

Changes in the condition of the inner surface of frog (and some other) skins can be demonstrated by observing the rate at which labelled phosphate is washed off. The loss is accelerated by deoxycorticosterone and by Ca-lack (165).

The entry of Na ions into the intact frog is increased following Na depletion (166). Entry is accelerated by the antidiuretic hormone (167). Cation and water movements have been reviewed [Ussing (168), (169); Huf (64)].

Although attempts have been made to formulate mechanisms of active Na movement these are still in the "NaX" stage. The fact that the transfer depends on K concentration has to be taken into account (see 64 and 170). Huf has discussed an adsorption-desorption "pump" which keeps up a high concentration of adsorbed K, with, in addition, a redox system of the kind discussed by Conway (171) and others for moving Na inwards. K ions are moved outwards across the skin; i.e., in the direction contrary to the active Na movement. In addition the skin cells can gain or lose K in abnormal solutions (Huf, *et al.* 170).

Frog skin is remarkable in having the ability to move Cl ions actively under conditions of Cl depletion. This can be accomplished by keeping the frog in a bicarbonate solution (166). The active movement of Cl has been shown to take place across the toad's skin; the net uptake of Cl from KCl solution cannot be accounted for by the electrochemical potential gradient, which is insufficient to cause net inward transfer.

An active movement of Li ions inwards across the skin has been described by Zerahn (172). Li competes with Na for transfer; in addition Li tends to accumulate in the skin cells to a level about six times the Na level in the cells. Exposure of the skin to Li ions causes a curious rhythmical variation of P.D. and resistance taking the form of a damped oscillation of about 0.3 periods/min. [Teorell (173)]. To maintain a high P.D. it has been noticed that Na or Li ions are indispensable. K, choline and ammonium ions depress P.D. and conductance.

The permeability to urea has been measured (174).

The Ocular and Cerebrospinal Fluids.—The study and interpretation of movements of materials into the compartments of the eye presents a complex problem because one has in addition to permeation, a secretion of fluid and drainage into Schlemm's canal. The subject has been reviewed by Davson (6, 175). Davson (176) has shown that the equilibration of a number of substances between the aqueous humour and plasma follows a first order equation but that it is rare for the final concentrations to be equal. The same is true of the cerebrospinal fluid. In general results for the aqueous and the cerebrospinal fluid are similar, but turnover between the aqueous and the plasma is increased by the secretory process, hence interchanges between plasma in the blood vessels and the cerebrospinal fluid are relatively more important than similar transfers in the eye. It is suggested that active Na movement is involved in the formation of both fluids. The distribution of CO_2 between plasma and the fluids has been studied (177). The permeability of the blood-brain barrier to sulphanilamide is little affected by a number of agents (Becker & Aird, 178). The permeability of the cornea has been studied and reviewed by Maurice (179, 180).

The composition of the vitreous humour of the eyes of marine invertebrates differs from a plasma ultrafiltrate; Na is 115 per cent and Mg 10 to 20 per cent of the ultrafiltrate level (Robertson, 181).

Mitochondria.—Until recently it was uncertain what factor controlled the swelling of mitochondria. Swelling often is a consequence of an interruption of metabolism, but addition of adenosine monophosphoric acid to a sucrose suspension also stops swelling; under these conditions there is no oxidative metabolism (182). Raaflaub correlates the swelling with the ATP content of the particles. Normally it is 0.05 μM/mg. of N; when it falls below 0.01 μM/mg. N, swelling starts (183) Adenosine diphosphoric acid and adenosine monophosphoric acid also break down. Respiration of mitochondria is inhibited by Ca. As Ca ions can be removed by complexing agents, among which ATP is included, there is a basis for control of respiration by the ATP level of the particles (184). Poisoning by DNP and azide have been studied. The former agent has a complex effect [Stanbury & Mudge (185)]; the latter reduces exchange of inorganic phosphate with the particle's store of ATP [Robertson & Boyer (186)].

Mitochondria behave osmotically like cells containing 40 to 50 per cent material which does not participate in the volume changes. Permeability to nonelectrolytes is correlated with the oil/water partition coefficient. Values of permeability constant are similar to those found for typical cells (238).

Tumour cells.—A comparison of the permeabilities of some neoplastic cells and of controls to a series of polyhydric alcohols showed no difference between the cells (187).

Ascites cells rapidly accumulate glycine (half time <3 min). The amount absorbed is related to the external concentration by the adsorption isotherm [Heinz (188)]. Treatment with pyridoxal or indole acetic acid causes increased glycine uptake and loss of K, Cl and water with gain of Na (189).

Plant cells.—Sutcliffe (190) uses a carrier mechanism to explain absorp-

tion of ions by plant tissue slices. Stewart & Millar (191) consider that uptake of Cs by leaves can be due to the ion becoming bound to sites (nucleic acid?) produced under the action of light.

Movements of Na and K between *Ulva Lactuca* or *Valonia* cells and the surroundings have been related to metabolism (192 to 195). In the dark the K of *Ulva* falls; the Na rises. Iodoacetate accelerates the rates of change in the dark but has no effect in light. This indicates that the ions are moved by a process which is potentiated either by photo synthesis or glycolysis. When the latter is blocked at the phosphoglyceraldehyde stage it fails to supply energy to the ion-transport system. Arsenate removes in part the iodoacetate inhibition because arseno-phosphoglyceric acid is spontaneously unstable and does not require an enzyme. The authors stress that combinations of poison plus metabolite can affect Na and K differently; for example, ATP or phosphoglycerate stops K loss without stopping Na gain. Pyruvate reduces Na gain without stopping K loss. Here there is no evidence for coupled movements as is also shown by K uptake from sucrose-leached cells being the same in either K plus sucrose or in sea water.

Microorganism.—Water content and ion accumulation of some bacteria have been studied by Cowie & Roberts (196). Centrifuged cells carry about 75 per cent water of which 10 to 20 parts are extracellular. The water space is accessible to sulphate, phosphate and alkali ions; the two former can be incorporated into intracellular materials. In *Escherichia coli* K, Rb, and Cs uptake is increased by metabolism to a level above that required to fill the water space; this extra amount is not readily washed from the cells. Glutamic acid is absorbed and metabolized as are cystine and methionine. (For glutamic acid see also 197.) Equilibration is completed within 5 min. A 1-for-1 uptake of glutamate and K by *Staphylococcus aureus* (198) recalls the behaviour of brain tissue. Glutamate absorption by the bacterium is stimulated by K. The phosphate of *Micrococcus pyogenes* is exchanged with a 70 min. half time (199, 200). The exchange can be inhibited by poisons; it has a maximum rate of pH 7. This was interpreted as showing that phosphate moves by formation of a complex which undergoes diffusion between interior and exterior.

The Kidney; Osmoregulation.—The question of whether one should regard formation of glomerular fluid as a filtration or a diffusion process has received arguments on both sides. Chinard, Vosburgh, & Enns (201) derive Starling's law from thermodynamic relations between osmoles and the activity of water. Garby (202) considers that the movement of the centre of gravity of a solution with respect to the membrane implies filtration. He points out that the distinction between flow and diffusion becomes meaningless when the pores are of molecular size. Any filtration will set up concentration gradients near the membrane which tend to limit the diffusion (Kuhn, 203).

It is not proposed to discuss active movement in the kidney tubules and the related organs of insects and marine species. [(See review by Winton (204)]. References to some papers dealing with these subjects, or with osmoregulation, are collected in the Table. The electrolyte contents of kidney

TABLE I

OSMOREGULATION AND RENAL FUNCTION

Material	Subject studied	Comment	Reference
Insect Malpighian tubules	Osmotic concentrations in haemolymph and urine	Urine hypotonic	Ramsay (205)
Insect Malpighian tubules	Excretion of Na, K and water	All secreted into tubules	Ramsey (206)
Sialis larvae	Permeability of cuticle to water, Cl. Ionic regulation	Low permeability attributed to wax. Na and K absorbed via gut, excreted in rectal fluid; some resorption	Shaw (207, 208)
Hydra	Osmoregulation	Na, K and Br all concentrated in tissue. Cells highly permeable to water	Lilly (209)
Eriocheir sinensis gills	Na movement	Active inward movement inhibited by CO_2, O_2— lack and poisons	Koch *et al.* (210)
Eriocheir sinensis gills	Na movement	Inhibition by anticholesterase	Koch (211)
Dog kidney	Osmotic concentrations in cells and urine	Osmoles in cells rise as osmoles in urine increase	Ullrich *et al.* (212)
Cat kidney	Glucose and phosphate resorption	Measurements	Eggleton & Schuster (213)
Mosquito larvae	Na uptake	Rate independent of K ions and external Na concentration	Treherne (214)
Kidney	Tubular secretion of phosphate	Discussion	Taugener *et al.* (215)
Kidney	Ca resorption	Depressed by DNP, azide and phlorizin	Chen & Neuman (216)

TABLE I—(*continued*)

Material	Subject studied	Comment	Reference
Kidney	Transport mechansim	Reviews	Selkurt (217), Mudge (218)
Kidney	Water and salt regulation	Symposium	(219)
Kidney	Excretion and resorption of diodrast and *p*-amino hippurate	Both resorbed in cat but excreted in rabbit	Josephson *et al.* (220)
Bullfrog	Urea transport	Active excretion, with upper limit. Can be poisoned	Forster (221)

and other tissue slices has been measured in both fresh and stored samples [Aebi (222)]. Storage usually leads to increase of tissue Na. Under metabolising conditions tissue K is maintained, so total cation rises. Oxygen lack causes gain of Na and water and loss of K (see also 223). Loss of K to a K-free medium is less when Ca ions are present than in their absence (222).

The exchange of K by slices of kidney is slowed, or made less complete by cooling, anaerobiosis, and poisons. On the other hand, a fraction of the total Na becomes more mobile under these conditions while another fraction becomes less mobile (224). This change of kinetics is similar to that which takes place in muscle Na when the tissue is stored (Harris, 63). It may mean that the balance between two successive processes, transport to the exterior surface, and desorption, has been altered. In the active cell transport keeps up with the desorption, giving a single rate constant for all the material; in a run down or cooled cell there is more rapid desorption of the surface layer because this is not appreciably replenished from the interior. After the surface has been cleared the slow loss from the interior, taking place via the surface, can be observed.

Accumulation of SO_4 by kidney slices takes place to 4 to 16 times the external concentration. The process appears to involve a metabolic reaction because it is reduced by cyanide, azide, anoxia or cooling. Optimum uptake of SO_4 from sucrose mixture is obtained in presence of 4 m.eq. K ions (225).

Tracer Cl movement from kidney cortex shows a fast component corresponding to 27 per cent extracellular space and an additional component with half time 1.5 min. aerobically and 3.3 min. anaerobically. Cellular Cl increases on cooling, poisoning, or in O_2-lack (226).

Eggs.—Fertilization of various eggs leads to permeability changes. Water is displaced from the *Fundulus* egg by the expansion of the perivitalline

space (230, 231). The salmon egg becomes less water permeable (227). Phosphate esters and rate of phosphate entry are altered (228, 229).

Gastric secretion.—This subject has been reviewed by Heinz & Öbrink (232). The rates of secretion of Cl and Br have been compared. The Br rate is about 1.5 times the Cl rate from a given concentration (233).

That the enzyme system which is responsible for secretion includes SH groups is made probable by the fact that reagents for these groups (*p*-chloromercuribenzoate, iodoacetamide) inhibit secretion (Davenport, *et al.* 234, 235). A hormonal control of secretion is shown by the increased secretion obtained 3 hr. after ACTH administration (236).

Conclusion

If one can draw any conclusion from the foregoing, it is that we need to know more about the location of ions in cellular systems, and the mechanism of their turnover, before we can interpret kinetic results. In particular, Na movement may often have an ion-exchange step; the rate of this need bear no relation to the supply of energy by metabolism, though it may reflect the dynamic state of adsorbing groups. The stimulating effect of raised K concentration on both metabolism and ion turnover in some tissues might be explained in this way.

LITERATURE CITED

1. *Electrolytes in Biological Systems* (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D. C., 243 pp., 1955)
2. *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
3. *Electrochemistry in Biology and Medicine* (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y., Chapman & Hall, Ltd., London, England, 369 pp., 1955)
4. *Ion Transport Across Membranes* (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
5. *Faraday Society Discussion on Membrane Phenomena* (In press)
6. Davson, H., *The Physiology of the Ocular and Cerebrospinal Fluids* (J. A. Churchill, Ltd., London, England, 400 pp., 1956)
7. LeFèvre, P. G., *Active Transport through Animal Cell Membranes*, Protoplasmatologia, **8**, 1–123 (Springer-Verlag, Vienna, Austria, 1955)
8. Harris, E. J., *Transport and Accumulation in Biological Systems* (Butterworth & Co. London, England 269 pp., 1956)
9. Johnson, F. H., Eyring, H., and Polissar, M. J., *The Kinetic Basis of Molecular Biology* (John Wiley & Sons, Inc., New York N. Y., 874 pp., 1954)
10. Wilde, W. S., *Ann. Rev. Physiol.*, **17**, 17–36 (1955)
11. Hodgkin, A. L., and Keynes, R. D., *J. Physiol. (London)*, **128**, 61–88 (1955)
12. Ling, G., *Am. J. Physical Med.*, **34**, 89–101 (1955)
13. Shaw, F. H., and Simon, S., *Australian J. Exptl. Biol. Med. Sci.*, **33**, 153–77 (1955)
14. Scatchard, G., *Ion Transport Across Membranes*, 128–43 (Clarke, H. T., Ed., Academic Press, Inc., New York, N.Y., 298 pp., 1954)
15. Parlin, R. B., and Eyring, H., *Ion Transport Across Membranes*, 103–118 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
16. McLennan, H., *Biochim. et Biophys. Acta*, **16**, 87–95 (1955)
17. McLennan, H., and Harris, E. J., *Biochem. J. (London)* **57**, 329–34 (1954)
18. Mudge, G., *Am. J. Physiol.*, **173**, 511–22 (1953)
19. Creese, R., *Proc. Roy. Soc. (London)* [B] **142**, 497–513 (1954)
20. Calkins, E., Taylor, I., and Hastings, A. B., *Am. J. Physiol*, **177**, 211–18 (1954)
21. Gold, G. L., and Solomon, A. K., *J. Gen. Physiol.*, **38**, 389–404 (1955)
22. Conway, E. J., and Carey, M., *Nature*, **175**, 773 (1955)
23. Harris, E. J., and Steinbach, H. B., *J. Physiol. (London)*, **133**, 385–401 (1956)
24. Carey, M., and Conway, E. J., *J. Physiol. (London)*, **125**, 232–50 (1954)
25. Harris, E. J., and Edwards, C., *Nature*, **175**, 262 (1955)
26. Prescott, D. M., and Zeuthen, E., *Acta Physiol. Scand.*, **28**, 77–94 (1953)
27. Flückiger, E., and Verzar, F., *Helv. Physiol. et Pharmacol. Acta*, **12**, 50–56 (1954)
28. Flückiger, E., and Verzar, F., *Helv. Physiol. et Pharmacol. Acta*, **12**, 57–62 (1954)
29. Barnes, J. M., Duff, J. I., and Threlfall, C. J., *J. Physiol. (London)*, **130**, 585–600 (1955)
30. Mudge, G., *Electrolytes in Biological Systems*, 112–22 (Shanes, A.M., Ed., Amer. Physiol. Soc., Washington, D. C., 243 pp., 1955)
31. Snell, F. M., *Electrochemistry in Biology and Medicine*, 284–300 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y., Chapman & Hall, Ltd., Lonon, England, 369 pp., 1955)

32. Rothstein, A., *Electrolytes in Biological Systems*, 65–100 (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D. C. 243 pp., 1955)
33. Rothstein, A., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 165–201 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
34. Lundegårdh, H., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 262–96 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
35. Scott-Russell, R., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 343–366 (Cambridge University Press, Cambridge, England 516 pp., 1954)
36. Epstein, E., *Electrolytes in Biological Systems*, 101–11 (Shanes, A.M., Ed., Amer. Physiol. Soc., Washington, D. C., 243 pp., 1955)
37. Epstein, E., and Leggett, J. E., *Am. J. Botany*, **41**, 785–91 (1954)
38. Pratley, J. N., and Rosene, H. F., *J. Cellular Comp. Physiol.*, **44**, 165–75 (1954)
39. Lott, J. R., and Rosene, J. F., *Am. J. Botany*, **43**, 69–72 (1956)
40. Wilbrandt, W., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 136–62 (Cambridge University Press, Cambridge, England 516 pp., 1954)
41. Brodsky, W. A., Rehm, W. S., Dennis, W. H., and Miller, D. G., *Science*, **121**, 302–03 (1955)
42. Rosenberg, T., and Wilbrandt, W., *Exptl. Cell Research.*, **9**, 49–67 (1955)
43. LeFèvre, P. G., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 118–35 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
44. Widdas, W. F., *J. Physiol.* (*London*) **125**, 163–80 (1954)
45. Wilbrandt, W., Frei, S. and Rosenberg, T. (In press)
46. Wilbrandt, W., *J. Cellular Comp. Physiol.*, **47**, 137–46 (1956)
47. Beloff-Chain, A., Chain, E. B., Catanzaro, R., and Longinotti, L., *Biochim. et Biophys. Acta*, **14**, 259–66 (1954)
48. Karvonen, M. J., and Räihä, N., *Acta Physiol. Scand.*, **31**, 194–202 (1954)
49. Alexander, D. P., Andrews, R. D., Huggett, A., Nixon, D. A., and Widdas, W. F., *J. Physiol.* (*London*), **129**, 352–66 (1955)
50. Alexander, D. P., Huggett, A., Nixon, D. A., and Widdas, W. F., *J. Physiol.* (*London*), **129**, 367–383 (1955)
51. Huxley, A., *Ion Transport Across Membranes*, 23–34 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
52. Hodgkin, A. L., and Huxley, A., *J. Physiol.* (*London*), **117**, 500–544 (1952)
53. Nachmansohn, D., and Wilson, I. B., *Ion Transport Across Membranes*, 35–64, (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
54. Nachmansohn, D., and Wilson, I. B., *Electrochemistry in Biology and Medicine*, 167–186 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London, England, 369 pp., 1955)
55. Hodgkin, A. L., and Keynes, R.D., *J. Physiol* (*London*), **128**, 28–60 (1955)
56. Simon, S., *Australian J. Exptl. Biol. Med. Sci.*, **33**, 179–88 (1955)
57. Caldwell, P. C., *J. Physiol.* (*London*), **132**, 35P (1956)
58. Grundfest, H., *Electrochemistry in Biology and Medicine*, 141–66 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London, England, 369 pp., 1955)

59. Kirschner, L. B., *J. Cellular Comp. Physiol.*, **45**, 61–87 (1955)
60. Linderholm, H., *Acta Physiol. Scand.*, **31**, 36–61 (1954)
61. Hogben, C. A. M., *Electrolytes in Biological Systems*, 176–204 (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D. C., 243 pp., 1955)
62. Hogben, C. A. M., *Am. J. Physiol.*, **180**, 641–49 (1955)
63. Harris, E. J., *Trans. Faraday Soc.*, **46**, 872–82 (1950)
64. Huf, E. G., *Electrolytes in Biological Systems*, 205–38 (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D.C., 243 pp., 1955)
65. Harris, E. J., *Active Transport and Secretion*. Symposia of the Society for Experimental Biology, No. 8, 228–41 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
66. Teorell, T., *Progress in Biophysics and Biophysical Chemistry*, **3**, 305–69 (Randall, J. T. and Butler, J. A., Eds., Pergamon Press, London, England, 386 pp., 1953)
67. Schlögl, R., *Z. Physikalische Chem.*, N.F. **1**, 305–39 (1954)
68. Hitchcock, D., *Electrochemistry in Biology and Medicine*, 6–17 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y.; Chapman & Hall, Ltd., London, England, 369 pp., 1955)
69. Hitchcock, D., *J. Gen. Physiol.*, **37**, 717–27 (1954)
70. Overbeek, J. T., *Progress in Biophysics and Biophysical Chemistry*, **6**, 57–84 (Butler, J. A., Ed., Pergamon Press, London, England, 274 pp., 1956)
71. Scatchard, G., *Electrochemistry in Biology and Medicine*, 18–32 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y.; Chapman & Hall, Ltd., London, England, 369 pp., 1955)
72. Sollner, K., *Electrochemistry in Biology and Medicine*, 33–64 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y.; Chapman & Hall, Ltd., London, England, 369 pp., 1955)
73. Sollner, K , Dray, S., Grim, E., and Neihof, R., *Electrochemistry in Biology and Medicine*, 65–90 (Shedlovsky, T., Ed., John Wiley & Sons, Inc., New York, N. Y.; Chapman & Hall, Ltd., London, England, 369 pp., 1955)
74. Sollner, K., Dray, S., Grim, E., and Neihof, R., *Ion Transport Across Membranes*, 144–88 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y.; 298 pp., 1954)
75. Juda, W., Marinsky, J. A., and Rosenberg, N. W., *Ann. Rev. Phys. Chem.*, **4**, 373–98 (1953)
76. Schlögl, R., *Z. Physikalische Chem.*, N.F. **3**, 73–102 (1955)
77. Kirkwood, J. G., *Ion Transport Across Membranes*, 119–27 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
78. von Bertalanffy, L., *Biophysik des Fliessgleichgewichts* (Vieweg & Sohn, Braunschweig, Germany, 56 pp., 1953)
79. Tobias, J. M., and Bryant, S. H., *J. Cellular Comp. Physiol.*, **46**, 163–82 (1955–56)
80. Robertson, J. D., *J. Biophys. Biochem. Cytol.*, **1**, 271–78 (1955)
81. Robertson, J. D., *Exptl. Cell. Research*, **8**, 226–29 (1955)
82. Geren, B. B., *Exptl. Cell Research*, **7**, 558–62 (1954)
83. Ottoson, D. F., Sjöstrand, F., Stenström, S., and Svaetichin, G., *Acta Physiol. Scand.*, **29**, Suppl. 106, 611–24 (1953)
84. Falk, G., and Gerard, R. W., *J. Cellular Comp. Physiol.*, **43**, 393–403 (1954)
85. Grundfest, H., *Electrolytes in Biological Systems*, 141–66 (Shanes, A. M., Ed., American Physiological Society, Washington, D. C., 243 pp., 1955)

86. Grundfest, H., Kao, C. Y., and Altamirano, M., *J. Gen. Physiol.*, **38,** 245–82 (1954)
87. Hodgkin, A. L., and Keynes, R. D., *J. Physiol. (London)*, **131,** 592–616 (1956)
88. Gossweiler, N., Kipfer, K., Poretti, G., and Rummel, W., *(Pflügers) Arch. ges. Physiol.*, **260,** 154–60 (1954–55)
89. Harris, E. J., and Nicholls, J., *J. Physiol. (London)*, **131,** 473–76 (1956)
90. Johnson, J. A., *Am. J. Physiol.*, **181,** 263–68 (1955)
91. Steinbach, H. B., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 438–52 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
92. Steinbach, H. B., *Am. J. Physiol.*, **167,** 284–87 (1954)
93. Barlow, J. C., and Manery, J. F., *J. Cellular Comp. Physiol.*, **43,** 165–92 (1954)
94. Caldwell, P. C., *J. Physiol. (London)*, **126,** 169–80 (1954)
95. Hill, A. V., *Proc. Roy. Soc. (London)*, [B]**144,** 1–22 (1955)
96. Shaw, J., *J. Exptl. Biol.*, **32,** 383–96 (1955)
97. Shaw, J., *J. Exptl. Biol.*, **32,** 664–80 (1955)
98. Hercus, V. M., McDowall, R. J. S., and Mendel, D., *J. Physiol. (London)*, **129,** 177–83 (1955)
99. Stolkowski, J., and Reinberg, A., *Arch. sci. physiol.*, **7,** 151–59 (1953)
100. Stolkowski, J., and Reinberg, A., *Arch. sci. physiol.*, **8,** 51–60 (1954)
101. Schatzmann, H., and Witt, P., *J. Pharmacol. Exptl. Therap.*, **112,** 501–08 (1954)
102. Harvey, S. C., *Am. J. Physiol.*, **183,** 559–64 (1955)
103. Holland, W. C., and Dunn, C. E., *Am. J. Physiol.*, **179,** 486–90 (1954)
104. Kraupp, O., *Arch. exptl. Path. Pharmakol.*, **228,** 271–87 (1956)
105. Born, G. V., and Bülbring, E., *J. Physiol. (London)*, **131,** 690–703 (1956)
106. Goldstein, M. S., Henry, W., Huddlestun, B., and Levine, R., *Am. J. Physiol.*, **173,** 207–11 (1953)
107. Goldstein, M. S., Mullick, V., Huddlestun, B., and Levine, R., *Am. J. Physiol.*, **173,** 212–16 (1953)
108. Wick, A. N., and Drury, D. R., *Am. J. Physiol.*, **173,** 229–32 (1953)
109. Park, C. R., and Johnson, L. H., *Am. J. Physiol.*, **182,** 17–23 (1955)
110. Park, C. R., Bornstein, J., and Post, R. L., *Am. J. Physiol.*, **182,** 12–16 (1955)
111. Huycke, E. J., and Kruhøffer, P., *Acta Physiol. Scand.*, **34,** 232–49 (1955)
112. Walaas, E., *Acta Physiol. Scand.*, **35,** 109–25 (1955)
113. Jervell, K. F., Walaas, E., and Walaas, O., *Acta Physiol. Scand.*, **35,** 321–37 (1955)
114. Clarkson, E. M., and Maizels, M., *J. Physiol. (London)*, **129,** 476–503 (1955)
115. Solomon, A. K., and Gold, G. L., *J. Gen. Physiol.*, **38,** 371–88 (1955)
116. Tosteson, D. C., *Electrolytes in Biological Systems*, 123–56 (Shanes, A. M., Ed., American Physiological Society, Washington, D. C., 243 pp., 1955)
117. Tosteson, D. C., and Robertson, J. S. *J. Cellular Comp. Physiol.*, **47,** 147–66 (1956)
118. Shaw, T. I., *J. Physiol. (London)*, **129,** 464–75 (1955)
119. Tosteson, D. C., Carlsen, E., and Dunham, E. T., *J. Gen. Physiol.*, **39,** 31–54 (1955)
120. Tosteson, D. C., *J. Gen. Physiol.*, **39,** 55–86 (1955)
121. Clarkson, E. M., and Maizels, M., *J. Physiol. (London)*, **129,** 504–12 (1955)
122. Maizels, M., *J. Physiol. (London)*, **125,** 263–77 (1954)
123. Maizels, M., *J. Physiol. (London)*, **132,** 414–41 (1956)

124. Ørskov, S. L., *Acta Physiol. Scand.*, **31**, 221–29 (1954)
125. Schatzmann, H. J., *Experientia*, **10**, 189 (1954)
126. Goodman, J. R., Marrone, L. H., and Squire, M. C., *Am. J. Physiol.*, **180** 118–120 (1955)
127. Eckel, R. E., *Am. J. Physiol.*, **179**, 632 (1954)
128. Love, W. D., Cronwich, J., and Burch, G., *J. Clin. Invest.*, **34**, 61–67 (1955)
129. Passow, H., and Tillmann, K., (*Pflügers*) *Arch. ges. Physiol.*, **262**, 23–36 (1956)
130. Passow, H., and Schütt, L., (*Pflügers*) *Arch. ges. Physiol.*, **262**, 193–206 (1956)
131. Joyce, C. R., Moore, H., and Weatherall, M., *Brit. J. Pharmacol.*, **9**, 463–70 (1954)
132. Green, J. W., *J. Cellular Comp. Physiol.*, **47**, 125–136 (1956)
133. Dunker, E., and Passow, H., (*Pflügers*) *Arch. ges. Physiol.*, **256**, 446–56 (1953)
134. Schweitzer, C. H., and Passow, H., (*Pflügers*) *Arch. ges. Physiol.*, **256**, 419–45 (1953)
135. Pletscher, A., van Planta, P., and Hunzinger, W. A., *Helv. Physiol. et Pharmacol. Acta*, **13**, 18–24 (1955)
136. Jonas, H., and Gourley, D. R., *Biochim. et Biophys. Acta*, **14**, 335–45 (1954)
137. Jonas, H., *Biochim. et Biophys. Acta*, **13**, 241–50 (1954)
138. Widdas, W., *J. Physiol.* (*London*), **127**, 318–27 (1955)
139. Brace, K. C., and Altland, P. D., *Am. J. Physiol.*, **183**, 91–94 (1955)
140. Love, W. E., *Biol. Bull.*, **105**, 128–32 (1953)
141. Hempling, H. G., *J. Cellular Comp. Physiol.*, **44**, 87–104 (1954)
142. Shanes, A. M., *J. Cellular Comp. Physiol.*, **43**, 87–98 (1954)
143. Dainty, J., and Krnjević, K., *J. Physiol.* (*London*), **128**, 489–503 (1955)
144. Emiroglu, F., *Arch. intern. physiol.*, **63**, 161–80 (1955)
145. Shanes, A. M., *J. Cellular Comp. Physiol.*, **43**, 99–106 (1954)
146. Shanes, A. M., and Berman, M. D., *J. Cellular Comp. Physiol.*, **45**, 199–240 (1955)
147. Shanes, A. M., and Berman, M. D., *J. Cellular Comp. Physiol.*, **45**, 177–98 (1955)
148. Krnjević, K., *J. Physiol.* (*London*), **128**, 473–88 (1955)
149. Stämpfli, R., and Nishie, K., *Helv. Physiol. et Pharmacol. Acta*, **14**, 93–104 (1956)
150. van Harreveld, A., and Russell, F. E., *J. Cellular Comp. Physiol.*, **43**, 335–46 (1954)
151. Hoyle, G., *J. Exptl. Biol.*, **30**, 121–35 (1953)
152. Mullins, L. J., *J. Cellular Comp. Physiol.*, **44**, 77–86 (1954)
153. Gray, J. A., and Sato, M., *J. Physiol.* (*London*), **129**, 594–607 (1955)
154. Coombes, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.* (*London*), **130**, 326–73 (1955)
155. Hodgkin, A. L., and Huxley, A., *J. Physiol.* (*London*), **121**, 403–414 (1953)
156. Foulkes, E. C., *J. Gen. Physiol.*, **38**, 425–30 (1955)
157. Conway, E. J., and Moore, P. T., *Biochem. J.* (*London*), **57**, 523–28 (1954)
158. Conway, E. J., Ryan, H., and Carton, E., *Biochem. J.* (*London*), **58**, 158–67 (1954)
159. Conway, E. J., and Kernan, R. P., *Biochem. J.* (*London*), **61**, 32–36 ((1955)
160. Conway, E. J., and Hingerty, D., *Biochem. J.* (*London*), **55**, 455–58 (1953)
161. Rothstein, A., and Demis, C., *Arch. Biochem. and Biophys.*, **44**, 18–29 (1953)
162. Schoffeniels, E., *Arch. intern. physiol.*, **63**, 361–65 (1955)
163. Schoffeniels, E., *Arch. intern. physiol.*, **63**, 513–30 (1955)

164. Kirschner, L. B., *J. Cellular Comp. Physiol.*, **45**, 89–102 (1955)
165. Schoffeniels, E., *Arch. intern. physiol.*, **63**, 366–75 (1955)
166. Jørgensen, C. B., Levi, H., and Zerahn, K., *Acta Physiol. Scand.*, **30**, 178–90 (1954)
167. Kalman, S. M., and Ussing, H. H., *J. Gen. Physiol.*, **38**, 361–70 (1954)
168. Ussing, H. H., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 407–22 (Cambridge University Press, Cambridge, England, 516 pp., 1954
169. Ussing, H. H., *Ion Transport Across Membranes*, 3–22 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
170. Huf, E., Wills, J., and Arrighi, M. F., *J. Gen. Physiol.*, **38**, 867–88 (1955)
171. Conway, E. J., *Intern. Rev. Cytol.*, **2**, 419–45 (1955)
172. Zerahn, K., *Acta Physiol. Scand.*, **33**, 347–58 (1955)
173. Teorell, T., *Acta Physiol. Scand.*, **31**, 268–84 (1954)
174. Garby, L., and Linderholm, H., *Acta Physiol. Scand.*, **32**, 264–70 (1955)
175. Davson, H., *Acta Physiol. Pharmacol. Néerl.*, **3**, 553–74 (1954)
176. Davson, H., *J. Physiol.* (*London*), **129**, 111–33 (1955)
177. Davson, H., and Luck, C. P., *J. Physiol.* (*London*), **132**, 454–64 (1956)
178. Becker, R. A., and Aird, R. B., *J. Cellular Comp. Physiol.*, **46**, 127–42 (1955)
179. Maurice, D. M., *Brit. J. Ophthalmol.*, **39**, 463–73 (1955)
180. Maurice, D. M., *Ophthalmol. Lit.*, **7**, 3–25 (1953)
181. Robertson, J. D., *J. Exptl. Biol.*, **30**, 277–96 (1953)
182. Fonnescu, A., and Davies, R. E., *Biochem. J.* (*London*), **61**, vi (1955)
183. Brenner-Holzach, O., and Raaflaub, J., *Helv. Physiol. et Pharmacol. Acta*, **12**, 242–52 (1954)
184. Raaflaub, J., *Helv. Physiol. et Pharmacol. Acta.*, **12**, C88 (1954)
185. Stanbury, S. W., and Mudge, G. H., *J. Biol. Chem.*, **210**, 949–964 (1954)
186. Robertson, H. E., and Boyer, P. D., *J. Biol. Chem.*, **214**, 295–305 (1955)
187. Lucké, B., Hempling, H. G., and Makler, J., *J. Cellular Comp. Physiol.*, **47**, 107–24 (1956)
188. Heinz, E., *J. Biol. Chem.*, **211**, 781–90 (1954)
189. Christensen, H. N., Riggs, T. R., and Coyne, B. A., *J. Biol. Chem.*, **209**, 413–27 (1954)
190. Sutcliffe, J. F., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 325–42 (Cambridge University Press, Cambridge, England, 516 pp., 1954).
191. Stewart, F. C., and Millar, F. K., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 367–406 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
192. Scott, G. T., and Hayward, H. R., *Electrolytes in Biological Systems*, 35–64 (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D.C., 243 pp., 1955)
193. Scott, G. T., and Hayward, H. R., *J. Gen. Physiol.*, **36**, 659–71 (1952–53)
194. Scott, G. T., and Hayward, H. R., *J. Gen. Physiol.*, **37**, 601–20 (1953–54)
195. Scott, G. T., and Hayward, H. R., *Biochim. Biophys. Acta*, **12**, 401–04 (1953)
196. Cowie, D. B., and Roberts, R. B., *Electrolytes in Biological Systems*, 1–34 (Shanes, A. M., Ed., Amer. Physiol. Soc., Washington, D.C., 243 pp., 1955)
197. Gale, E. F., *Active Transport and Secretion*, Symposia of the Society for Experi-

mental Biology, No. 8, 242–53 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
198. Davies, R., Folkes, J. P., Gale, E. F., and Bigger, L. C., *Biochem. J. (London)*, **54,** 430–37 (1953)
199. Mitchell, P., and Moyle, J. M., *J. Gen. Microbiol.*, **9,** 257–72 (1953)
200. Mitchell, P., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 254–61 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
201. Chinard, F. P., Vosburgh, G. J., and Enns, T., *Am. J. Physiol.*, **183,** 221–34 (1955)
202. Garby, L., *Acta Physiol. Scand.*, **35,** 88–92 (1955)
203. Kuhn, W., *Z. Electrochem.*, **55,** 207–17 (1951)
204. Winton, F. R., *Ann. Rev. Physiol.*, **18,** 225–52 (1956)
205. Ramsay, J. A., *J. Exptl. Biol.*, **31,** 104–13 (1954)
206. Ramsay, J. A., *J. Exptl. Biol.*, **32,** 200–16 (1955)
207. Shaw, J., *J. Exptl. Biol.*, **32,** 330–52 (1955)
208. Shaw, J., *J. Exptl. Biol.*, **32,** 353–82 (1955)
209. Lilly, S. J., *J. Exptl. Biol.*, **32,** 423–39 (1955)
210. Koch, H. J., Evans, J., and Schicks, E., *Mededelingen van de Koninklijke Vlaamse Academie voor Wetenschappen, Letteren, en Schone Kunsten*, **15,** 3–16 (1954)
211. Koch, H. J., *Recent Advances in Cell Physiology*, 15–27 (Kitching, J. A., Ed., Butterworth & Co., Ltd., London, England, 206 pp., 1954)
212. Ullrich, K. J., Drenckhahn, F. O., and Jarausch, K. H., (*Pflügers*) *Arch. ges. Physiol.*, **261,** 62–77 (1955)
213. Eggleton, M. G., and Schuster, S., *J. Physiol. (London)*, **124,** 613–22 (1954)
214. Treherne, J. E., *J. Exptl. Biol.*, **31,** 386–401 (1954)
215. Taugener, R., Bubnoff, M., and Braun, W., (*Pflügers*) *Arch. ges. Physiol.*, **258,** 133–48 (1954)
216. Chen, P. S., and Neumann, W. F., *Am. J. Physiol.*, **180,** 623–31 (1955)
217. Selkurt, E. E., *Physiol. Revs.*, **34,** 287–333 (1954)
218. Mudge, G. H., *Ion Transport Across Membranes*, 75–102 (Clarke, H. T., Ed., Academic Press, Inc., New York, N. Y., 298 pp., 1954)
219. Symposium on Water and Salt Regulation, *Arch. sci. physiol.*, **7,** C5-C161 (1953); **8,** C162–C298 (1954)
220. Josephson, B., Grieg, A., Kakossaios, G., and Kallas, J., *Acta Physiol. Scand.*, **30,** 11–21 (1953–54)
221. Forster, R. P., *Amer. J. Physiol.*, **179,** 372–77 (1954)
222. Aebi, H., *Helv. Physiol. et Pharmacol. Acta*, **11,** 96–121 (1953)
223. Davies, R. E., *Active Transport and Secretion*, Symposia of the Society for Experimental Biology, No. 8, 453–75 (Cambridge University Press, Cambridge, England, 516 pp., 1954)
224. Whittam, R., and Davies, R. E., *Biochem. J. (London)*, **56,** 445–53 (1954)
225. Deyrup, I. J., and Ussing, H. H., *J. Gen. Physiol.*, **38,** 599–612 (1955)
226. Whittam, R., *J. Physiol. (London)*, **131,** 542–54 (1955)
227. Kao, C. Y., Chambers, R., and Chambers, E. L., *J. Cellular Comp. Physiol.*, **44,** 447–61 (1954)
228. Kao, C. Y., and Chambers, R., *J. Exptl. Biol.*, **31,** 139–50 (1954)
229. Prescott, D. M., *J. Cellular Comp. Physiol.*, **45,** 1–12 (1955)

230. Brooks, S. C., and Chambers, E. L., *Biol. Bull.*, **106**, 279–96 (1954)
231. Chambers, E. L., and White, W. E., *Biol. Bull.*, **106**, 297–307 (1954)
232. Heinz, E., and Öbrink, K. J., *Physiol. Revs.*, **34**, 643–73 (1954)
233. Heinz, E., Öbrink, K. J., and Ulfendahl, H., *Gastroenterology*, **27**, 98–112 (1954)
234. Davenport, H. W., Chavré, V. J., and Davenport, V. D., *Am. J. Physiol.*, **182**, 221–26 (1955)
235. Davenport, H. W., Chavré, V. J., and Davenport, V. D., *Am. J. Physiol.*, **184**, 1–10 (1956)
236. Villareal, R., Ganong, W. F., and Gray, S. J., *Am. J. Physiol.*, **183**, 485–94 (1955)
237. Sjöstrand, F. S., and Rhodin, J., *Exptl. Cell Research*, **4**, 426–56 (1953)
238. Tedeschi, H., and Harris, D. L., *Arch. Biochem. and Biophys.*, **58**, 52–67 (1955)

DEVELOPMENTAL PHYSIOLOGY[1,2]

By L. G. Barth

Zoology Department, Columbia University, New York, N. Y.

Recently investigators in the field of developmental physiology have stressed the role of the proteins in the process of differentiation. Their studies show that not only do new proteins develop with time and become localized in the embryo but, in addition, the inductors of the various parts of the nervous system are closely associated with pentose nucleoproteins. Thus we are beginning to acquire firmer bases for chemical embryology both on a descriptive level and for a causal analysis.

Studies on the induction of the primary embryonic axis are organized about a stimulus-response mechanism whereby various tissues and extracts of tissues are applied as stimuli to the presumptive epidermis of the amphibian gastrula. The responses of the epidermis are classified according to the structures which are induced, and the generally accepted classification of these structures is as follows: archencephalic, when forebrain, eye, or nasal placode are present; deuterocephalic, when midbrain, hindbrain, or otocyst are induced to form; spinocaudal, when spinal cord or somites are present. Recently a fourth response of the epidermis whereby only mesodermal structures are elicited has been added. Guinea pig or rat liver preparations generally are used to induce archencephalic structures, guinea pig kidney preparations for spinocaudal inductions, and bone marrow is used for the induction of purely mesodermal structures.

The several investigators are in partial agreement in that all favor two-factor hypotheses with some interaction and some gradient distribution of the factors. There is considerable discussion and criticism of the various interpretations of the nature and action of the inductors.

The specific inductive capacity of living mouse liver, kidney, spleen, and bone marrow was tested on gastrular ectoderm of *Triturus pyrrhogaster* (1). Bone marrow induced mesodermal structures, while liver induced brain. The outer layer of the cortex of the kidney induced cephalic structures, while the inner layer and the medulla induced spinocaudal structures (2).

Extracts of guinea pig liver and kidney with 0.14 M NaCl were tested and found to induce chiefly archencepahlic and spinocaudal structures respectively (3, 4, 5). A further fractionation of the 0.14 M NaCl extracts by precipitation with streptomycin sulfate resulted in a more intense induction with higher specificity as compared with the nonprecipitible fraction (3, 4). These results indicate that the pentose nucleoproteins are chiefly

[1] The survey of the literature pertaining to this review was completed in April 1956.

[2] The following abbreviations are used in this chapter: DNA (deoxyribonucleic acid); RNA (ribonucleic acid); DNP (dinitrophenol); ACTH (adenocorticotropic hormone)

responsible for the specific inductions. However the pentose nucleic acid moiety may not be necessary, since almost complete removal by ribonuclease acting upon phosphate, saline, or acetate extracts of guinea pig kidney and rat liver does not change the inductive capacity of these extracts (6). The inductive capacity of 0.14 M NaCl extracts of guinea pig kidney is changed from spinocaudal induction to archencephalic induction by treatment of the extracts with heat or with 3 M NaCl [Yamada & Takata (5)]. These authors offer a two-factor hypothesis involving a dorso-ventral mediator (Mdv) which induces archencephalic structures and a cephalo-caudal mediator (Mcc) which together with Mdv induces spinocaudal structures. Mdv plus a little Mcc induces deuterocephalic structures. Both Mdv and Mcc are present in kidney extracts and heat inactivates Mcc so that Mdv remains to induce archencephalic structures. As an alternate interpretation they suggest that spinocaudal induction occurs when the protein complex is in the native state and upon denaturation with heat it becomes an archencephalic inductor.

Toivonen & Saxen (7, 8) have succeeded in obtaining an inductor from bone marrow which is highly specific for mesoderm inductions such as notochord, myotomes, and pronephros, but induces no neural structures. When they combine bone marrow inductor with liver inductor they obtain spinal cord in addition to the forebrain and hindbrain induced by the liver alone. They formulate a two-factor hypothesis with a neuralizing agent (N) and a mesodermalizing agent (M). (N) alone induces archencephalic structures which vary according to the concentration of (N). (N) plus some (M) induces midbrain and hindbrain, while (N) plus more (M) induces spinal cord.

Nieuwkoop's theory of an activation of the ectoderm to form prosencephalon followed by a transforming factor from the chorda mesoderm receives support from a numbers of papers (9 to 14). Regional differences in the inductive capacity of the median strip of the archenteron roof were demonstrated in *Ambystoma mexicanum* by placing four different regions between two pieces of gastrular ectoderm (13). The removal of a strip of ectoderm from different stages of gastrulation shows that first the ectoderm is activated to form prosencephalon but after contact with more posterior regions of the chorda mesoderm the same ectoderm becomes transformed into more posterior parts of the nervous system (14).

In contrast to the evidence that inductors are protein in character, Holtfreter (15) shows that some inductors, at least, will diffuse through agar and cellophane, and Kawakami & Okano (16) obtain very good inductions of brain and nasal placode by treating the ventral marginal zone with Holtfreter's solution at pH 3.1–3.4. Indeed Pasteels (17) criticizes the use of adult tissues in the search for normal inductors and defends the interpretation of a nonspecific induction upon a reacting ectoderm. His experiments show that the ectoderm is activated to form hindbrain, otocyst, notochord, somites, and pronephros by centrifugation.

Grafts of inductor labelled with C^{14} lose some of the labelled compound to

host tissues (18). Two studies on the inactivation of inductors show that trypsin and chymotrypsin suppress inducing ability in *Triturus* and that dead organizer loses its ability to induce in *Rana pipiens* (19, 20).

In my opinion the time has come to analyse the roof of the archenteron for the specific inducing substances found in liver, kidney, and bone marrow.

Inductions of specific structures.—The inductive relationship between mouse metanephrogenic mesenchyme and epithelial elements are such that neither component by itself will differentiate into tubules [Grobstein (21, 22)]. While no other mesenchyme will induce the epithelial element to form a tube, the induction of tubules in the metanephrogenic mesenchyme is effected by spinal cord and sub-mandibular salivary epithelium. The induction occurs when the components are separated by a membrane and dead tissues lose their inductive capacity.

The role of the spinal cord in the formation of the vertebrae is demonstrated by transplantation studies in amphibians and by *in vitro* combinations of spinal cord and somites of mouse embryos (23, 24, 25). Grobstein & Holtzer (25) show that the basal plate induces the somite to form cartilage and contact is not necessary. Dead basal plate fails to induce.

The induction of amphibian tapetum to form neural retina by contact with the epithelium of the ear vesicle is independent of the central nervous system and will occur when the optic vesicle and ear vesicle are grafted below the somites (26).

A study of the competence of the ectoderm of *Ambystoma* to form a lens and the inductive ability of the optic vesicle shows that loss of competence is gradual (27). A new and intriguing experiment by Holtfreter (28) demonstrates the conversion of an induced tail into a limb. Analyses of xenoplastic inductions confirm the generalization that the induced structure has the same characteristics as that of the donor from which the tissue was taken (29 to 32). Balinsky (29) points out that relative position and size of structures may be changed. Baltzer (33) finds more than usual participation of non-competent tissue of *Bombinator* in the formation of the balancer together with *Triton* tissue.

Directed cell migration and cell affinities.—After induction of the amphibian neural plate various cell types segregate and exhibit coordinated movements (34, 35). Townes & Holtfreter (34) report that neural cells placed on epidermis migrate to the interior; epidermal cells migrate outward and spread over other cell types; after dissociation cells reaggregate according to type. Spiegel (36) found amphibian cells failed to aggregate in antiserum but did so in normal serum. Similar results were obtained with dissociated sponge cells (37).

The differentiation of a mixture of dissociated cells of chick wing bud and mesonephros results in the formation of mesonephric tubules (38). The possibility that older cells of the wing bud are transformed into mesonephric tubules is suggested. Although Grobstein (39) points up the significance of size of explants from blastoderms on their ability to differentiate, Cavanaugh

(40) is able to isolate single cells from the chick heart and finds that the atrium and ventricle cells pulsate at 1.61 and 0.90 pulsations per second respectively.

Morphogenetic movements of explants of the hybrid gastrula *Rana pipiens* ♀ × *Rana sylvatica* ♂ are normal in ventral ectoderm but abnormal in presumptive notochord (41). The failure to gastrulate may be a result of the inability of the notochord to converge medially. That morphogenetic movements of the foregut of the chick are not the result of a high mitotic activity is reported by Bellairs (42).

Although embryonic cells show specific affinities for like cells, Wolff and Weniger (43) are able to fuse mouse gonad with duck gonad *in vitro*. The cells of the two classes mingle freely. Other tissues behave similarly (44). The whole question of compatibility of tissues in reviewed by Greene (45) who points out that both cancer in a certain stage of development and embryonic tissue are able to grow xenoplastically, while adult tissues will not.

Further evidence for the development of specific proteins comes from the effect of anti-sera on developing chick embryos. Ebert (46) reviews his studies on the localization of actin and actin plus myosin, while Johnson & Leone (47) find that anti-chicken sera stop growth at the primitive streak stage and anti-actomyosin inhibits general growth and particularly the development of the heart. On the other hand anti-actin and antiglobulin X have little effect and anti-myogen appears to stimulate growth.

Studies on the incorporation of large molecules and even carbon particles into the cells of blastoderms are reviewed by Schechtman (48). Additional work demonstrates that heterologous serum proteins pass from the blood of the hen into the ovum (49) and that fowl antisera of *Salmonella pullorum* or *Brucella abortus* injected into the yolk sac appears in the blood of the chick at hatching (50). The transfer of organ specific substances from blood to mesonephros is indicated by an increased mitotic index of the mesonephros and the liver after intravenous injection of mesonephric material (51). The incorporation and distribution of the labelled amino acids glycine, methionine into *Xenopus* and labelled methionine in chick embryos is significantly different in different tissues (52, 53).

The ability of embryonic cells to incorporate large molecules and even carbon particles may be important in embryonic induction if the normal inductors turn out to be pentose nucleoproteins. Possibly microsomes and even mitochondria may be transferred from inductor to competent tissue, although some of the membrane studies do not support this idea.

After fertilization of the sea urchin egg some proteins become more sensitive to trypsin while others show a decreased precipitability with salts [Giardina & Monroy (54)]. Also the sea urchin egg proteins behave differently when treated with animalizing and vegetalizing agents (55). The former induce a decrease in viscosity of the fibrillar proteins, making them more sensitive to the denaturing action of urea. Conversely vegetalizing agents cause an increase in viscosity and render the proteins more resistant to urea. The denaturing effects of animalizing agents is reversible in the presence of

adenosine-triphosphate. Similar results are obtained with frog egg proteins [Ranzi (56)].

An electrophoretic analysis of hen egg yolk indicates four fractions in livetin and two fractions in lipovitellin (57, 58).

Chemical differentiation.—As Løvtrup (59) concludes in a comprehensive study on chemical differentiation during amphibian development, it is difficult to obtain more than correlations between morphological changes and chemical changes. When however an analysis of enzymes is combined with experimental modifications of the embryo we gain more knowledge regarding mechanisms. Boell, Greenfield & Shen (60) combined a study of the localization of choline esterase in the optic lobes of *R. pipiens* larvae with the extirpation of the eye and find that the specific activity decreases chiefly in those regions believed to consist largely of synapses. Moog & Richardson (61) injected cortisones into 10 to 18 day chick embryos and obtained a precocious accumulation of duodenal phosphatase and an early differentiation of the epithelial cells of the duodenum. Sawyer (62) correlates reflex activity of *Ambystoma* larvae with choline esterase activity and finds that di-isopropyl fluorophosphate inhibits choline esterase irreversibly. The larva can regenerate the enzyme however.

The normal development of enzymes has been investigated in amphibia by Løvtrup (59) (acid phosphatase, alkaline phosphatase, amylase, cathepsin, tripeptidase, trypsin); by Shen, Greenfield & Boell (63) (cholinesterase in frog brain); and by Sippel (64) (cholinesterase in heart); in the chick embryo by Richardson, Berkowitz & Moog (65) (nonspecific esterase activity of duodenum); by Konigsberg & Herrman (66) (alkaline phosphatase in muscle); by Rudnick & Waelsch (67) (glutamotransferase in nervous system).

With regard to other substances, determinations of DNA in nuclei of various cell types in the developing sea urchin show no differences in amount (68). The DNA content of developing eggs of *A. mexicanum* increases from 0.1 μg. during early cleavage to 100 μg. at 60 days with a period (stage 37 to 40) during which no synthesis appears to occur (59). A slower increase in RNA with no significant fluctuations was measured. RNA has also been measured in the cells of the spinal cord of chick embryos from 2 to 14 days [Hughes (69)].

The rate of accumulation of collagen in chick muscle is compared with the accumulation of actomyosin and found to be the same (70). A chromatographic study of fluorescent substances present in various amphibian eggs at different stages of development was made by Leonardi (71).

General metabolism.—Cohen (72) investigated anaerobiosis in *R. pipiens* gastrulae, concluding that at 20°C. the gastrula is under partially anaerobic conditions and a substance is present in reduced state. Teidemann & Teidemann (73) describe defects obtained when *Triton* gastrulae are treated with HCN. The effects of KCN and dinitrophenol on the frog egg are reported by Ikushima (74). The antagonism between DNP and azide on the apyrase activity of extracts of toad embryos and the oxygen consumption of

intact embryos was studied (75, 76). Similar results were obtained with fish embryos (77). The pattern of oxidation of reduced dyes by cleavage, gastrula and neurula stages of *Rhacophorus* and *Triturus* embryos is correlated with morphogenetic movements of the cells (78). A method for measuring respiration of tissue cultures on a small glass cylinder by the Cartesian diver is described (79).

Antimetabolites and other compounds.—Several investigators have studied the effects of antimetabolites and the reversal by normal metabolites. Concerning purine antimetabolites, Liedke, Engelman & Graff (80) tested 37 compounds as inhibitors of development of *R. pipiens* eggs. Some compounds inhibited early cleavage, while others interfered with neurulation. Waddington, Feldman & Perry (81) used 8-azaguanine and benzimidazole on early chick and newt embryos and describe cellular degeneration in the region of the primitive streak and reduced head region. Benzimidazole inhibits cleavage of the ascidian egg (82).

Hörstadius & Gustafson (83) compared the effects of 8-chloroxanthine and beta-phenyllactic acid on sea urchin development. Since both inhibit bilateral development the effect may be a result of surface-active properties and not antimetabolic. The authors report animalizing and vegetalizing effects of various antimetabolites and suggest that physical properties of the compounds may be important (84).

Amino acid antagonists have both general and specific effects. Segregation of the somites at the four somite stage of the chick embryo is specifically inhibited by omega-bromoallylglycine. Reversal occurs with leucine, valine, methionine, phenyl alanine, and lysine [Hermann, Konigsberg & Curry (85)]. Ethionine inhibits growth of chick embryos and also the incorporation of methionine labelled with S^{35} (86). Four day chick embryos injected with asaserine are inhibited in growth and have defects in the appendicular skeleton and beak (87).

Wilde (88) found specific effects of beta-2-thienyl alanine on ectomesenchyme and phenyl lactic acid on pigment cell differentiation in isolated neural crest of *Ambystoma maculatum*. Phenyl alanine itself stimulates ventral ectoderm to form pigment cells. Selective inhibition of cleavage indifferent regions of *R. pipiens* eggs by sulphydryl inhibitors suggests a localization of sulphydryl compounds within the egg [Barth (89)].

The abnormalities produced in chick embryos by excess vitamin A include a stoppage of growth [Herbertson (90)], while injections of trypaflavine, colchicine, and saponin result in exencephaly (91). In amphibia 10 per cent sucrose inhibits the differentiation of the pituitary body (92). Abnormal development follows treatment of eggs and blastoderms of *Drosophila melanogaster* with ultrasonic waves (93). A method for following the accumulation of lithium in amphibian embryos by autoradiography has been developed (94).

The effects of changes in oxygen tension on differentiation and growth have been examined by Nelson (95) who finds that 50 per cent of chick blas-

toderms are injured at six atmospheres air pressure, and Cook & Krum (96) report that the growth of young mice is retarded in decompression chambers and high altitudes. Lowered oxygen tensions or exposure to 4°C. during irradiation (200 r) has a protective action on the subsequent development of fertilized *Triton alpestris* eggs (97). Chick embryos are protected against the effects of irradiation by beta-mercaptoethylamine (98). Proliferation of Schwann cells, fibroblasts and other cells is retarded by x-irradiation in the rat (99).

Propyl-thiouracil administered to *Ambystoma punctatum* larvae induced tumors of thyroid tissues in the gills [Copenhaver (100)]. These tumors will not grow when transplanted to normal larvae. Thiouracil does not change the amount of radioiodine (I^{131}) incorporated into *R. pipiens* tadpoles but does cause a greater retention (101).

Special processes in development.—Colwin & Colwin (102) have presented a new analysis of fertilization. They observe a long acrosome filament projecting from the head of the sperm through the jelly to the surface of the egg. The egg cone forms and flows around this filament while the sperm enters the cone by some as yet unknown means. Ito & Leuchtenberger (103) correlate DNA content of clam spermatozoa with the ability to penetrate and activate eggs. In human sperm a high degree of variability of DNA is found in cases of suspected infertility (104). The liberation of zinc from starfish sperm during increased motility induced by histidine is reported (105). An extensive cytological and cytochemical study of *Artemia* spermatozoa was made by Fautrez-Firlefyn & Fautrez (106, 107).

Studies on partially fertilized sea urchin eggs with partial breakdown of cortical granules show that sperm may enter any surface where the granules are intact (108, 109, 110). An electric current will cause breakdown of cortical granules without activating the egg (111).

Detailed cytochemical and cytological studies of the egg are available for the fish, *Lebistes reticulatus* (112), the guinea pig and rabbit (113) and various rodents [Dalcq (114)]. The structure of the jelly surrounding the sea urchin egg and the amphibian egg have been investigated by Monroy (115) and by Minganti (116).

The mechanism of cleavage in the newt's egg was studied by Selman & Waddington (117), who conclude that a gelation at the furrow plus a contraction of this gel satisfies observations. On the other hand various agents which induce cell division in *Chaetopterus* produce a measurable decrease in the viscosity of the cortex [Hoilbrunn & Wilson (118)]. Fujii (119) proposes that the transfer of zinc from the nucleolus of the sea urchin egg to the chromosomes and spindle is important in mitosis.

Stimulation of mitotic activity in the rat kidney by ligature of the ureter was reported by Fautrez & Roels (120) and increased mitosis of the *Ambystoma* fin epidermis by spinal cord grafts by Overton (121). A burst of mitotic activity in the tail of *R. pipiens* tapoles at stage 22 is as yet unexplained [Di Berardino (122)].

A number of antimitotic agents have been studied. Reduced ribonuclease inhibits cell division in amphibian eggs and onion root tip. Some protection is obtained with ribonucleic acid (123, 124, 125). Substances produced by fatigued muscles and also extracts of starfish and fish ovaries inhibit cleavage of *Chaetopterus* eggs (126, 127). During senility amitosis is observed in mouse cerebellum and human liver (128).

The interrelationship between the nucleus and cytoplasm during differentiation is being examined by a variety of approaches. Very important are the findings of Briggs & King (129, 130) that nuclei from the gastrula differ from each other as tested by implantation into an enucleated egg. Thus we may now speak of nuclear differentiations during development. The development of hybrids has been examined in a number of cases in frogs [Moore (131)] and in sea urchins [Baltzer & Bernhard (132)]. The conclusion appears to be that the egg cytoplasm has a specific biochemical makeup and that the introduction of a foreign sperm does not change this until the gastrula stage. Enucleation of cells of the sea urchin effectively prevents them from participating in development even though they may undergo division. An exception may be that enucleated animal cells interact with the nucleated vegetal cells to produce a better developed larva than the vegetal cells alone [Hörstadius, Lorch & Danielli (133, 134)].

The addition of extra nuclear material to an egg by a cross between triploid and diploid axolotls results in low fertility and abnormal development [Fankhauser & Humphrey (135)].

Early development of vertebrates.—New studies on the phenomenon of ingression during cleavage of the amphibian egg by Ballard (136) are interpreted to mean that ingression is essentially an artifact resulting from the stained surface being drawn into the cleavage furrow. After carbon particle marking of the duck blastoderm a migration of the markings to the posterior margin of the blastoderm and an involution of the marks occurs [Lutz (137)]. Peter's polyinvagination hypothesis is criticized adversely.

Experimental studies in the interrelationship between the endoderm and the lateral mesoderm of *T. pyrrhogaster* show that each is dependent upon the other for complete differentiation [Takamoto (138), Okada (139, 140)]. Endoderm free larvae possess supernumerary limbs, lack genital ridges and have a poorly developed pronephros. The endoderm explanted without mesoderm fails to differentiate. In *Fundulus* transplantations of parts of the embryonic shield into the gastrula result in regional differentiations of eye and oral epithelium when anterior parts of the shield are transplanted and spinal cord, notochord, intestine, and striated muscle when posterior portions are used [Oppenheimer (141, 142)]. The uninvaginated prechordal plate of *Triturus* gastrula when isolated first possesses the notochord potency and induces spinal cords but after culture in Holtfreter's solution it loses the ability to form notochord and acquires the ability to induce forebrain [Takaya (143)].

In his excellent analysis of the organizer center of the early chick embryo

Spratt (144, 145) demonstrates a single chorda center which induces posterior prospective notochord to differentiate and two bilaterally arranged somite centers which control differentiation of the prospective somites posterior to them. Removal of these centers results in a failure in the differentiation of posterior mesoderm.

Mangold (146) has explanted the epidermis of *Triton* neurula together with adhering mesoderm and observes the differentiation of skin, balancer, forelimb, pronephros, and heart but no nervous system, notochord, somites, or endodermal structures. In another paper Mangold makes a detailed analysis of the structure of the head after removal of parts of the anterior medullary plate (147).

The potencies of the cranial neural crest of *A. maculatum* include cartilage, dentin, balancer, striated muscle, Schwann cells, and ectomesenchyme [Wilde (148)]. Removal of the neural crest in about 25 somite chick embryos results in absence of the neurons in the sacral autonomic ganglia and the nerve of Remak (149). Preganglionic fibers come from the neural tube.

Lyon (150) has made a study of the development of otoliths in mice and Witschi (151) discusses the relation of the bronchial columella of the ear of various species of *Rana* to underwater hearing. A comprehensive investigation of the differentiation of the transplanted nasal placode of *T. alpestris* and the outgrowth of the nerves to the spinal cord was made by Teichmann (152). Hamburger (153) has summarized trends in neuroembryology and, with co-workers, presents evidence that the active fraction of nerve stimulating tumors is a pentosenucleoprotein (154).

Zwilling (155) exchanged the apical ectodermal caps of chick wing and leg buds and found that the resulting structure is determined by the mesodermal component. Amprino & Camosso (156) conclude from extirpation experiments that determination of the limb bud proceeds from proximal to distal. Xenoplastic transplants of *Triton* limb region from neurula will not develop but at Stage 38 normal development is obtained (157).

Detwiler (158) shows that the ventro-lateral musculature of *Ambystoma* comes from the somites and not from the somatic mesoderm as claimed for the chick.

Rappaport (159) presents good evidence by removal of heart or pronephric pouches of *R. pipiens* that the pronephros functions by taking fluids from the coelom and not by filtration through the glomerulus. The heart mesoderm of *A. punctatum* comes from mesoderm lateral to the hindbrain [Wilens (160)]. A dual origin of the tail somites from posterior neural plate and from cells lateral to the slit blastopore is described for *R. pipiens* by Smithberg (161).

The ultimobranchial body of *Xenopus laevis* develops from the sixth visceral pouch and does not store iodine nor form thyroid tissues (162). *In vitro* differentiation of the chick pancreas was studied by Black & Comolli (163). Investigations on the development of pigment patterns include skin grafts in fetal rats [Rawles (164)]; transplantation of amphibian ventral

mesoderm to somite region with interference of normal pattern [Finnegan (165)]; an analysis of breeding of chimeras of black and white axolotls [Church (166)] and an experimental study of the barred pigment pattern in axolotl [Lehman (167)].

Invertebrate embryology.—Recent advances in this field stress localization of substances within developing systems. Thus Bonner, Chiquoine & Kolderie (168) demonstrate high alkaline phosphatase in presumptive stalk cells and little in presumptive spore cells in *Dictyostelium discoideum*. Distribution and behavior of nonstarch polysaccharides is also determined. Also in this form Sussman & Lee (169) show interaction of variants and wild type aggregations separated by agar membranes. Other studies include effects of environmental factors, development, and the nitrogen metabolism of various stages of mutants, the kinetics of growth (170 to 173).

Weisz (174, 175) reports induction of division and regenerative reorganization in *Stentor* by parabiotic fusions.

In the realm of sea urchin experimentation Runnström (176) presents a comprehensive analysis of early differentation including antigenicity tests, incorporation of C^{14} and N^{15}, enzymatic activity, and distribution of mitochondria. Hörstadius (177) has added experimental modifications to study differential dye reduction in *Paracentrotus lividus* blastula and finds a close correlation between reduction gradients and animal and vegetal gradients.

Investigations on the development of the eggs of molluscs, worms, and ascidians have resulted in a description of the development of isolated blastomeres of *Mytilus edulis* by Rattenbury & Berg (178). Berg (179) also finds the cytochrome oxidase activity of the posterior blastomeres of *Ciona* intestinalis to be 2.7 times that of anterior blastomeres. Reverberi (180) reports the localization of Janus green staining mitochondria in the posterior blastomeres of *Phallusia mamillata*. Alkaline phosphatase is usually localized in the vegetal half of this ascidian but appears in the animal half after isolation (181).

Localization of cytochrome oxidase and succinodehydrogenase occurs in the D cell and the micromeres of the eight cell stage of *Tubifex rivulorum* (182). In centrifuged eggs these enzymes are found in the heavier mitochondrial layer. Glycogen is localized in the vegetal blastomeres and finally in the endoderm (183).

In *Bithymia codiella* cytochrome oxidase is present at the animal pole while lipides are in the vegetal blastomeres (184), and in *Physarivularis* the enzyme is in the animal region (185).

These localizations will need to be interpreted in light of the fact that the granules of some mosaic eggs may be relocalized without causing abnormalities in development. Thus the yellow pigment normally found in the muscle of *Styela* may be relocated and appear in the nervous system after centrifugation of the egg.

Nieuwkoop (186) finds that lithium ions applied to the eggs of *Ascidia malaca* directly after fertilization causes exogastrulation, and Farinella-

Ferruzza (187) reports that development of the notochord, muscles, and mesenchyme is not affected but brain and sense organs are lacking. Raven, De Roon & Stadhouders (188) used heat shock on *L. stagnalis* eggs to produce exogastrulae with reduplications of the eye and apical plate. Treatment of *P. rivularis* eggs with sodium azide results in disturbances in gastrulation and head malformations (189).

Physiology of regeneration.—A number of researches support the concept that innervation is necessary for regeneration: Kamrin & Singer (190, 191) barbel of *Ameiurus nebulosus* and tail of *Anolis carolinensis;* Holtzer, Holtzer & Avery (192) tail vertebrae of *Amblystoma opacum;* Van Stone (193) hind limb of *Rana sylvatica* tadpoles. In the latter both the number of nerve fibers per unit area and regeneration capacity were found to increase from proximal to distal regions. Wright (194) reports an interesting exception in which the taste organs of *Triturus viridescens* maintained their histological structure for a year in the orbit.

Limbs will not regenerate in absence of the pituitary but injections of ACTH temporarily restores regeneration [Schotté & Chamberlain (195)]. Induction of accessory forelimbs in urodeles has been obtained by exposure to ultraviolet [Butler & Blum (196)] and by implantation of frog carcinoma or kidney [Ruben (197)].

The proximal end of the humerus is able to induce regeneration of radius and ulna in reversed proximo-distal limb implants in *A. punctatum* [Butler (198)]. Almost normal regression, blastema formation, and regeneration occurs. Dick (199) finds that innervation of these reversed limbs is primarily from nerves VI and VII.

Other works report regeneration of the tectum opticum in urodeles with restoration of the visuomotor responses [Weimer (200)]; re-establishment of function after transection of the cord in urodeles [Piatt (201)]; regeneration of an iris followed by regeneration of a lens in *Triturus viridescens* [Stone (202)]; differing rates of lens regeneration in urodeles [Reyer & Stone (203)]; chemical properties of alpha-amino ketones which inhibit tail regeneration in *X. laevis* [Lehmann, *et al.* (204)].

Invertebrate regeneration has been studied by Steinberg (205) who correlates migration of cells with rate of regeneration in *Tubularia;* by Kurtz & Schrank (206) whose electrical measurements of regenerating earthworms support the idea that regeneration is halted by a critical voltage; by Stéphan-Dubois (207) who describes the migration of neoblasts in regenerating oligochaetes; and by Bodenstein (208) who finds that adult *Periplaneta americana* which normally do not regenerate legs can do so if induced to molt by parabiotic fusion with a nymph.

Recent books.—Since the last review we have gained a comprehensive technical analysis of development edited by Willier, Weiss & Hamburger (209) and a treatise of the principles of development on a graduate level by Waddington (210). Together with Raven's (211) outline of developmental physiology and several more specialized treatments of embryology (212 to

215) the student as well as the investigator should find no dearth of material and ideas. For the premedical student and the zoology major Witschi (216) has written a book presenting developmental concepts as arising from descriptive and experimental vertebrate embryology.

Summary.—As a result of the important experiments of Briggs & King we may look forward to the time when the nuclei of various cell types will be proved to differ from one another. We will then be able to speak of genetically different strains of cells in the organism. These different strains would arise first as a result of cytoplasmic localization in the egg and later embryonic induction would stimulate nuclear differentiation. A feedback mechanism would provide progressive differentiation. It may well be that the concept of plasma genes will no longer be necessary.

And if we accept the general trend of thinking of the inductors as pentose nucleoproteins what better specific compounds could we wish for as activators of specific nuclear genes which produce the visible changes we call differentiation. Such cases as the effects of lithium and sulphocyanide on differentiation of sea urchin cells at first present a difficulty, but if we accept Ranzi's hypothesis (backed by many measurements) that these substances cause an alteration in the proteins of the egg then we may again assume a specific effect of these proteins on the nuclear genes which feed back into the cytoplasm new proteins. Obviously, in this case, the endodermal and ectodermal inductors must be very similar since they are converted into each other. The archencephalic and spinocaudal inductors, too, may be very similar since kidney extracts inducing spinocaudal structures may be converted into archencephalic inductors by denaturing agents. Further if we assume that the gene stimulating proteins in the cytoplasm are species specific we have a reasonable interpretation of the abnormal development of hybrids on the basis of analog inhibition. The early localization of actomyosin in the heart blastoderm speaks well for a protein necessary for differentiation. The effects of anti-sera would be more readily interpreted if they simply prevented differentiation without killing the cells.

In any case real progress toward a comprehensive theory of development has been made by the investigations reviewed here and by as many more which had to be omitted. With continued activity along present lines of research we may confidently predict a better understanding of the intricate mechanics of development.

LITERATURE CITED

1. Kawakami, I., and Mifune, S., *Mem. Fac. of Sci., Kyūsū Univ.* [E], **2**, 22–30 (1955)
2. Mifune, S., *Mem. Fac. Sci. Kyūsū Univ.*, [E], **2**, 13–19 (1955)
3. Hayashi, Y., *Embryologia*, **3**, 57–67 (1956)
4. Yamada, T., and Takata, K., *Embryologia*, **3**, 69–79 (1956)
5. Yamada, T., and Takata, K., *J. Exptl. Zool.*, **128**, 291–332 (1955)
6. Hayashi, Y., *Embryologia*, **2**, 145–62 (1955)

7. Toivonen, S., and Saxén, L., *Exptl. Cell Research*, Suppl. 3, 346–57 (1955)
8. Toivonen, S., and Saxén, L., *Ann. Acad. Sci. Fennicae*, Series A, IV, 3–29 (1955)
9. Nieuwkoop, P. D., and Nigtevecht, G. V., *J. Embryol. Exptl. Morphol.*, **2**, 175–93 (1954)
10. Nieuwkoop, P. D., *et al.*, *Koninkl. Ned. Akad. Wetenschap. Proc.* [C]**58**, 219–27 (1955)
11. Hori, R., and Nieuwkoop, P. D., *Koninkl. Ned. Akad. Wetenschap. Proc.*, [C], **58**, 266–72 (1955)
12. Nieuwkoop, P. D., *Exptl. Cell Research*, Suppl. 3, 262–73 (1955)
13. Sala, S. J. M., *Koninkl. Ned. Akad. Wetenschap. Proc.*, [C], **58**, 635–47 (1955)
14. Eyal-Giladi, H., *Arch. Biol.*, **65**, 179–259 (1954)
15. Holtfreter, J., *Exptl. Cell Research*, Suppl. 3, 188–209 (1955)
16. Kawakami, I., and Okano, H., *Mem. Fac. Sci., Kyūsū Univ.*, [E], **2**, 1–11 (1955)
17. Pasteels, J., *J. Embryol. Exptl. Morphol.*, **2**, 122–48 (1954)
18. Ficq, A., *J. Embryol. Exptl. Morphol.*, **2**, 194–203 (1954)
19. Yamada, T., and Takata, K., *Exptl. Cell Research*, Suppl. 3, 402–13 (1955)
20. Smith, A. E. S., and Schechtman, A. M., *J. Exptl. Zool.*, **125**, 265–84 (1954)
21. Grobstein, C., *Aspects of Synthesis and Order in Growth*, 233–56 (Princeton University Press, Princeton, N. J., 274 pp., 1955)
22. Grobstein, C., *J. Exptl. Zool.*, **130**, 319–39 (1955)
23. Detwiler, S. R., and Holtzer, H., *Bull. Hosp. Joint Diseases*, **15**, 114–23 (1954)
24. Grobstein, C., and Parker, G., *Proc. Soc. Exptl. Biol. Med.*, **85**, 477–481 (1954)
25. Grobstein, C., and Holtzer, H., *J. Exptl. Zool.*, **128**, 333–53 (1955)
26. Detwiler, S. R., and Van Dyke, R. H., *J. Exptl. Zool.*, **126**, 135–56 (1954)
27. Liedke, K. B., *J. Exptl. Zool.*, **130**, 353–71 (1955)
28. Holtfreter, J., *J. Exptl. Zool.*, **129**, 623–48 (1955)
29. Balinsky, B. I., *J. Embryol. Exptl. Morphol.*, **3**, 93–120 (1955)
30. Chen, P. S., *Arch. Entwicklungsmech. Organ.*, **147**, 634–86 (1955)
31. Wagner, G., *J. Embryol. Exptl. Morphol.*, **3**, 160–88 (1955)
32. Durante, M., *Riv. Biol. Perugia*, **47**, 417–38 (1955)
33. Baltzer, F., and Chen, P. S., *Arch. Vererbungsforsch., Sozialanthropol. Rassenhyg.*, **29**, 352–59 (1954)
34. Townes, P. L., and Holtfreter, J., *J. Exptl. Zool.*, **128**, 53–120 (1955)
35. Feldman, M., *J. Embryol. Exptl. Morphol.*, **3**, 251–55 (1955)
36. Spiegel, M., *Biol. Bull.*, **107**, 149–55 (1954)
37. Spiegel, M., *Biol. Bull.*, **107**, 130–48 (1954)
38. Trinkaus, J. P., and Groves, P. W., *Proc. Natl. Acad. Sci. U. S.*, **41**, 787–95 (1955)
39. Grobstein, C., *Ann. N. Y. Acad. Sci.*, **60**, 1095–106 (1955)
40. Cavanaugh, M. W., *J. Exptl. Zool.*, **128**, 573–89 (1955)
41. Gregg, J. R., and Klein, D., *Biol. Bull.*, **109**, 265–70 (1955)
42. Bellairs, R., *J. Embryol. Exptl. Morphol.*, **3**, 242–50 (1955)
43. Wolff, E., and Weniger, J. P., *J. Embryol. Exptl. Morphol.*, **2**, 161–71 (1954)
44. Wolff, E., *Bull. Soc. Zool. France*, **79**, 357–68 (1954)
45. Greene, H. S. N., *Biological Specificity and Growth*, 177–94 (Princeton University Press, Princeton, N. J., 233 pp., 1955)
46. Ebert, J. D., *Aspects of Synthesis and Order in Growth*, 69–112 (Princeton University Press, Princeton, N. J., 274 pp., 1955)

47. Johnson, I. S., and Leone, C. A., *J. Exptl. Zool.*, **130**, 515–54 (1955)
48. Schechtman, A. M., *Biological Specificity and Growth*, 3–31 (Princeton University Press, Princeton, N. J., 233 pp., 1955)
49. Knight, P. F., and Schechtman, A. M., *J. Exptl. Zool.*, **127**, 271–304 (1954)
50. Brierley, J., and Hemmings, W. A., *J. Embryol. Exptl. Morphol.*, **4**, 34–41 (1956)
51. Andres, G., *J. Exptl. Zool.*, **130**, 221–49 (1955)
52. Waddington, C. H., and Sirlin, J. L., *J. Embryol. Exptl. Morphol.*, **3**, 340–47 (1954)
53. Feldman, M., and Waddington, C. H., *J. Embryol. Exptl. Morphol.*, **3**, 44–58 (1955)
54. Giardina, G., and Monroy, A., *Exptl. Cell Research*, **8**, 466–73 (1955)
55. Ranzi, S., and Citterio, P., *Pubbl. staz. zool. Napoli*, **25**, 201–40 (1954)
56. Ranzi, S., *Inst. Lombardo Sci. Lettere, Rendiconti, Classe Sci.*, **89**, 200–23 (1955)
57. Gorini, I., and Lanzavecchia, G., *Inst. Lombardo Sci. e Lettere, Rendiconti, Classe Sci.*, **88**, 951–59 (1955)
58. Lanzavecchia, G., *Inst. Lombardo Sci. Lettere, Rendiconti, Classe Sci.*, **89**, 224–42 (1955)
59. Løvtrup, S., *Compt. rend. trav. lab. Carlsberg, Sér. chim.*, **29**, 261–314 (1955)
60. Boell, E. J., Greenfield, P., and Shen, S. C., *J. Exptl. Zool.*, **129**, 415–51 (1955)
61. Moog, F., and Richardson, D., *J. Exptl. Zool.*, **130**, 29–56 (1955)
62. Sawyer, C. H., *J. Exptl. Zool.*, **129**, 561–78 (1955)
63. Shen, S. C., Greenfield, P., and Boell, E. J., *J. Comp. Neurol.*, **102**, 717–44 (1955)
64. Sippel, T. O., *J. Exptl. Zool.*, **128**, 165–84 (1955)
65. Richardson, D., Berkowitz, S. D., and Moog, F., *J. Exptl. Zool.*, **130**, 57–69 (1955)
66. Konigsberg, I. R., and Hermann, H., *Arch. Biochem. and Biophys.*, **55**, 534–45 (1955)
67. Rudnick, D., and Waelsch, H., *J. Exptl. Zool.*, **129**, 309–26 (1955)
68. McMaster, R. D., *J. Exptl. Zool.*, **130**, 1–27 (1955)
69. Hughes, A., *J. Embryol. Exptl. Morphol.*, **3**, 305–25 (1955)
70. Hermann, H., and Barry, S. R., *Arch. Biochem. and Biophys.*, **55**, 526–33 (1955)
71. Leonardi, M. C., *Inst. Lombardo Sci. Lettere, Rendiconti, Classe Sci.*, **88**, 1025–33 (1955)
72. Cohen, A. I., *J. Embryol. Exptl. Morphol.*, **3**, 77–85 (1955)
73. Tiedemann, H., and Tiedemann, H., *Z. Naturforschung*, **9b**, 371–80 (1954)
74. Ikushima, N., *Mem. Coll. of Sci., Univ. Kyoto*, [B] **21**, 15–21 (1954)
75. Maruyama, K., *Arch. Biochem. and Biophys.*, **60**, 74–81 (1956)
76. Ishida, J., Uramoto, M., and Maruyama, K., *J. of the Fac. Sci., Univ. Tokyo*, **7**, 399–409 (1955)
77. Maruyama, K., and Ishida, J., *Annot. Zool. Japon.*, **28**, 131–36 (1955)
78. Ikushima, N., *Mem. Coll. Sci., Univ. Kyoto*, **20**, 151–56 (1953)
79. Danes, B. S., *Compt. Rend. trav. lab. Carlsberg, Ser. Chim.*, **29**, 209–21 (1955)
80. Liedke, K. B., Engelman, M., and Graff, S., *J. Exptl. Zool.*, **127**, 201–19 (1954)
81. Waddington, C. H., Feldman, M., and Perry, M. M., *Exptl. Cell Research*, Suppl. 3, 366–80 (1955)

82. Waddington, C. H., and Mancuso, V., *Exptl. Cell Research*, **9**, 269–371 (1955)
83. Hörstadius, S., and Gustafson, T., *J. Embryol. Exptl. Morphol.*, **2**, 216–26 (1954)
84. Gustafson, T., and Hörstadius, S., *Exptl. Cell Research*, Suppl. 3, 170–80 (1955)
85. Herrmann, H., Konigsberg, U. R., and Curry, M. F., *J. Exptl. Zool.*, **128**, 359–77 (1955)
86. Feldman, M., and Waddington, C. H., *J. Embryol. Exptl. Morphol.*, **3**, 44–58 (1955)
87. Dagg, C. P., and Karnofsky, D. A., *J. Exptl. Zool.*, **130**, 555–72 (1955)
88. Wilde, C. E., Jr., *J. Morphol.*, **97**, 313–44 (1955)
89. Barth, L. J., *J. Embryol. Exptl. Morphol.*, **4**, 1–20 (1956)
90. Herbertson, M. A., *J. Embryol. Exptl. Morphol.*, **3**, 355–65 (1955)
91. Ancel, P., *J. Embryol. Exptl. Morphol.*, **3**, 335–54 (1955)
92. Driscoll, W. T., and Eakin, R. M., *J. Exptl. Zool.*, **129**, 149–76 (1955)
93. Counce, S. J., and Selman, G. G., *J. Embryol. Exptl. Morphol.*, **3**, 121–41 (1955)
94. Ficq, A., *J. Embryol. Exptl. Morphol.*, **2**, 204–15 (1954)
95. Nelson, O. E., *J. Morphol.*, **96**, 359–79 (1955)
96. Cook, S. F., and Krum, A. A., *J. Exptl. Zool.*, **128**, 561–72 (1955)
97. Peters, T., *Strahlentherapie*, **98**, 628–39 (1955)
98. Wolff, E., and Kirrman, J. M., *Compt. rend. soc. biol.*, **148**, 1629–31 (1954)
99. Edds, M. V., Jr., *J. Exptl. Zool.*, **129**, 225–47 (1955)
100. Copenhaver, W. M., *J. Exptl. Zool.*, **129**, 291–307 (1955)
101. Money, W. L., Lucas, V., and Rawson, R. W., *J. Exptl. Zool.*, **128**, 411–21.
102. Colwin, A. L., and Colwin, L. H., *J. Morphol.*, **97**, 543–68 (1955)
103. Ito, S., and Leuchtenberger, C., *Chromosoma*, **7**, 328–39 (1955)
104. Leuchtenberger, C., Weir, D. R., Schrader, F., and Murmanis, L., *J. Lab. Clin. Med.*, **45**, 851–64 (1955)
105. Fujii, T., Utida, S., Mizuno, T., and Nanao, S., *J. Fac. Sci., Univ. Tokyo*, **7**, 335–45 (1955)
106. Fautrez-Firlefyn, N., and Fautrez, J., *Arch. biol. (Liége)*, **66**, 195–222 (1955)
107. Fautrez-Firlefyn, N., and Fautrez, J., *Arch. biol. (Liége)*, **65**, 497–530 (1954)
108. Allen, R. D., *Exptl. Cell Research*, **6**, 403–24 (1954)
109. Allen, R. D., and Hagström, B., *Exptl. Cell Research*, **9**, 157–67 (1955)
110. Allen, R. D., and Hagström, B., *Exptl. Cell Research*, Suppl. 3, 1–15 (1955)
111. Allen, R. D., Lundberg, A., and Runnström, J., *Exptl. Cell Research*, **9**, 174–80 (1955)
112. Vakaet, L., *Arch. biol. (Liége)*, **66**, 1–73 (1955)
113. De Geeter, L., *Arch. biol. (Liége)*, **65**, 363–436 (1954)
114. Dalcq, A. M., *Compt. rend. soc. biol.*, **148**, 1332–73 (1954)
115. Monroy, A., *Exptl. Cell Research*, Suppl. 3, 252–54 (1955)
116. Minganti, A., *Ricerca sci.*, **24**, 3–6 (1954)
117. Selman, G. G., and Waddington, C. H., *J. Exptl. Biol.*, **32**, 700–33 (1955)
118. Heilbrunn, L. V., and Wilson, W. L., *Protoplasma*, **44**, 377–84 (1955)
119. Fujii, T., *J. Fac. Sci., Univ. Tokyo*, **7**, 313–25 (1955)
120. Fautrez, J., and Roels, H., *Arch. biol. (Liége)*, **65**, 461–96 (1954)
121. Overton, J., *J. Exptl. Zool.*, **130**, 433–83 (1955)
122. DiBerardino, M., *Experientia*, **11**, 152–56 (1955)
123. Ledoux, L., LeClerc, J., and Vanderhaeghe, F., *Nature*, **174**, 793–94 (1954)

124. Brachet, J., *Acta Biochim. et Biophys.*, **16**, 611–12 (1955)
125. Brachet, J., and Ledoux, L., *Exptl. Cell Research*, Suppl. 3, 27–39 (1955)
126. Heilbrunn, L. V., and Wilson, W. L., *Pubbl. staz. zool. Napoli*, **27**, 295–99 (1955)
127. Heilbrunn, L. V., Chaet, A. B., Dunn, A., and Wilson, W. L., *Biol. Bull.*, **106**, 158–68 (1954)
128. Andrew, W., *J. Gerontol.*, **10**, 1–12 (1955)
129. King, T. J., and Briggs, R., *Proc. Natl. Acad. Sci. U. S.*, **41**, 321–25 (1955)
130. Briggs, R., and King, T. J., *Biological Specificity and Growth*, 207–33 (Princeton University Press, Princeton, N. J., 233 pp., 1955)
131. Moore, J. A., *Advances in Genet.*, **7**, 139–82 (1955)
132. Baltzer, F., and Bernhard, M., *Exptl. Cell Research*, Suppl. 3, 16–26 (1955)
133. Hörstadius, S., Lorch, I. J., and Danielli, J. F., *Expt. Cell Research*, **4**, 263–74 (1953)
134. Lorch, I. J., Danielli, J. F., and Hörstadius, S., *Exptl. Cell Research*, **4**, 253–62 (1953)
135. Fankhauser, G., and Humphrey, R. R., *J. Exptl. Zool.*, **126**, 33–58 (1954)
136. Ballard, W. W., *J. Exptl. Zool.*, **129**, 77–98 (1955)
137. Lutz, H., *J. Embryol. Exptl. Morphol.*, **3**, 59–76 (1955)
138. Takamoto, K., *J. Inst. Polytech., Osaka City Univ.*, **4**[D], 51–60 (1953)
139. Okada, T. S., *Annot. Zool. Japon.*, **28**, 210–14 (1955)
140. Okada, T. S., *Mem. Coll. Sci., Univ. of Kyoto*, [B] **21**, 1–22 (1954)
141. Oppenheimer, J. M., *J. Exptl. Zool.*, **128**, 525–59 (1955)
142. Oppenheimer, J. M., *J. Exptl. Zool.*, **129**, 649–81 (1955)
143. Takaya, H., *Annot. Zool. Japon.*, **26**, 202–07 (1953)
144. Spratt, N. T., Jr., *Aspects of Synthesis and Order in Growth*, 209–31 (Princeton University Press, Princeton, N. J., 274 pp., 1955)
145. Spratt, N. T., Jr., *J. Exptl. Zool.*, **128**, 121–63 (1955)
146. Mangold, O., *Arch. Entwicklungsmech. Organ.*, **147**, 131–70 (1954)
147. Mangold, O., *Arch. Entwicklungsmech. Organ.*, **148**, 123–78 (1955)
148. Wilde, C. E., Jr., *J. Exptl. Zool.*, **130**, 573–95 (1955)
149. Yntema, C. L., and Hammond, W. S., *J. Exptl. Zool.*, **129**, 375–413 (1955)
150. Lyon, M. F., *J. Embryol. Exptl. Morphol.*, **3**, 213–29 (1955)
151. Witschi, E., *J. Morphol.*, **96**, 497–511 (1955)
152. Teichmann, H., *Arch. Entwicklungsmech.*, **148**, 218–62 (1955)
153. Hamburger, V., *Biochemistry of the developing Nervous System*, 52–71 (Academic Press Inc., New York, N. Y., 1954)
154. Cohen, S., Levi-Montalcini, R., and Hamburger, V., *Proc. Am. Assoc. Cancer Research*, **1**, 9–33 (1954)
155. Zwilling, E., *J. Exptl. Zool.*, **128**, 423–41 (1955)
156. Amprino, R., and Camosso, M., *J. Exptl. Zool.*, **129**, 453–93 (1955)
157. Durante, M., *Riv. Biol.*, **46**, 533–40 (1954)
158. Detwiler, S. R., *J. Exptl. Zool.*, **129**, 45–75 (1955)
159. Rappaport, R., Jr., *J. Exptl. Zool.*, **128**, 481–87 (1955)
160. Wilens, S., *J. Exptl. Zool.*, **129**, 579–605 (1955)
161. Smithberg, M., *J. Exptl. Zool.*, **127**, 397–425 (1954)
162. Saxén, L., and Toivonen, S., *J. Embryol. Exptl. Morphol.*, **3**, 376–84 (1955)
163. Black, L., and Comolli, R., *Arch. d'Anat. microscop. morphol. Exptl.*, **43**, 276–81 (1954)

164. Rawles, M. E., *American J. Anat.*, **97**, 79–128 (1955)
165. Finnegan, C. V., *J. Exptl. Zool.*, **128**, 453–79 (1955)
166. Church, G., *J. Morphol.*, **96**, 565–77 (1955)
167. Lehman, H. E., *J. Elisha Mitchell Sci. Soc.*, **70**, 218–21 (1954)
168. Bonner, J. T., Chiquoine, A. D., and Kolderie, M. Q., *J. Exptl. Zool.*, **130**, 133–57 (1955)
169. Sussman, M., and Lee, F., *Proc. Natl. Acad. Sci. U. S.*, **41**, 70–78 (1955)
170. Bradley, S. G., Sussman, M., and Ennis, H. L., *J. Protozool.*, **3**, 33–38 (1956)
171. Sussman, M., *J. Gen. Microbiol.*, **13**, 295–309 (1955)
172. Sussman, M., *Biol. Bull.*, **110**, 91–95 (1956)
173. Gregg, J. H., Hackney, A. L., and Krivanek, J. O., *Biol. Bull.*, **107**, 226–35 (1954)
174. Weisz, P. B., *J. Cell. Comp. Physiol.*, **46**, 517–28 (1955)
175. Weisz, P. B., *J. Exptl. Zool.*, **131**, 137–62 (1956)
176. Runnström, J., *Verhandl. deut. Zool. Ges., Tübingen*, 32–68 (1954)
177. Hörstadius, S., *J. Exptl. Zool.*, **129**, 249–56 (1955)
178. Rattenbury, J. C., and Berg, W. E., *J. Morphol.*, **95**, 393–414 (1954)
179. Berg, W. E., *Biol. Bull.*, **110**, 1–7 (1956)
180. Reverberi, G., *Experientia*, **12**, 55–60 (1956)
181. Minganti, A., *Pubbl. staz. zool. Napoli*, **25**, 438–43 (1954)
182. Carrano, F., and Palazzo, F., *Riv. Biol.*, **47**, 193–201 (1955)
183. Carrano, F., *Ricerca Sci.*, **25**, 1–6 (1955)
184. Carmela, A., *Ricerca Sci.*, **25**, 1–6 (1955)
185. Mancuso, V., *Ricerca Sci.*, **25**, 1–4 (1955)
186. Nieuwkoop, P. D., *Pubbl. staz. zool. Napoli*, **24**, 101–41 (1953)
187. Farinella-Ferruzza, N., *Pubbl. staz. zool. Napoli*, **26**, 42–54 (1955)
188. Raven, C. P., De Roon, A. C., and Stadhouders, A. M., *J. Embryol. Exptl. Morphol.*, **3**, 142–59 (1955)
189. Mancuso, V., *Riv. Biol.*, **47**, 203–07 (1955)
190. Kamrin, R. P., and Singer, M., *J. Morphol.*, **96**, 173–87 (1955)
191. Kamrin, R. P., and Singer, M., *J. Exptl. Zool.*, **128**, 611–27 (1955)
192. Holtzer, H., Holtzer, S., and Avery, G., *J. Morphol.*, **96**, 145–71 (1955)
193. Van Stone, J. M., *J. Morphol.*, **97**, 345–91 (1956)
194. Wright, M. R., *J. Exptl. Zool.*, **129**, 357–73 (1955)
195. Schotté, O. E., and Chamberlain, J. L., *Rev. suisse Zool.*, **62**, 253–79 (1955)
196. Butler, E. G., and Blum, H. F., *J. Natl. Cancer Inst.*, **15**, 877–89 (1955)
197. Ruben, L. N., *J. Exptl. Zool.*, **128**, 29–51 (1955)
198. Butler, E. G., *J. Morphol.*, **96**, 265–81 (1955)
199. Dick, J. D., *J. Morphol.*, **96**, 301–31 (1955)
200. Wiemer, F. K., *Arch. Entwicklungsmech. Organ.*, **147**, 560–633 (1955)
201. Piatt, J., *J. Exptl. Zool.*, **129**, 177–207 (1955)
202. Stone, L. S., *J. Exptl. Zool.*, **129**, 505–33 (1955)
203. Reyer, R. W., and Stone, L. S., *J. Exptl. Zool.*, **129**, 257–89 (1955)
204. Lehman, F. E., Weber, W., Aebi, H., Bäumler, J., and Erlenmyer, H., *Helv. Physiol. et Physiol. Acta*, **12**, 147–80 (1954)
205. Steinberg, M. S., *Biol. Bull.*, **108**, 219–34 (1955)
206. Kurtz, I., and Schrank, A. R., *Physiol. Zool.*, **28**, 322–30 (1955)
207. Stéphan-Dubois, F., *Bull. Biol. France et Belg.*, **88**, 183–247 (1954)

208. Bodenstein, D., *J. Expll. Zool.*, **129**, 209–24 (1955)
209. Willier, B. H., Weiss, P. A., and Hamburger, V., *Analysis of Development* (W. B. Saunders, Philadelphia, 735 pp., 1955)
210. Waddington, C. H., *Principles of Embryology* (Geo. Allen and Unwin, Ltd., London, England, 510 pp., 1956)
211. Raven, C. P., *An Outline of Developmental Physiology* (McGraw-Hill Book Co., Inc., New York, N. Y., 216 pp., 1954)
212. Rudnick, D., Ed., *Aspects of Synthesis and Order in Growth* (Princeton University Press, Princeton, N. J., 274 pp., 1954)
213. Butler, E. G., Ed. *Biological Specificity and Growth* (Princeton University Press, Princeton, N. J., 233 pp., 1955)
214. Barth, L. G., and Barth, L. J., *The Energetics of Development* (Columbia University Press, New York, N. Y., 125 pp., 1954)
215. Barigozzi, C., Ranzi, S., and Tonzig, S., *Problemi di Sviluppo* (Casa Editrice Ambrosiana, Milan, Italy, 283 pp., 1954)
216. Witschi, E., *Development of Vertebrates* (W. B. Saunders Company, Philadelphia, Pa., 588 pp., 1956)

PHYSIOLOGICAL ASPECTS OF HEAT AND COLD[1]

By Jan Bělehrádek

Departments of Biology and Physiology, Middlesex Hospital Medical School, London, England

The author of this chapter has been invited to revise the literature on the general physiological aspects of the action of temperature for the 20 years which have elapsed since the publication of the first edition of his relevant book (1). Well over 3,000 papers in this field have been published since then, and only a small fraction can be mentioned here. These should be regarded as a representative sample illustrating the general trends prevailing during this period. The two most important are (*a*) a descriptive study of the temperature response, requirements, and tolerance of various physiological properties and functions, and (*b*) an attempt to obtain a closer insight into the intimate cellular chemomechanisms by analytic studies of the responses of living systems to temperature variations.

Thermic Properties

The effect of body size upon the time required to attain equilibrium with the external temperature has been illustrated by experiments on the fruit fly (*Drosophila*), where 30 secs. suffice to stabilize the wing rhythm at a new temperature (2), and on bacteria in which flash-heat exposures of 0.5 sec. duration were applied, when only 10^{-5} sec. were lost in heat conduction (3; cf. also 164). The combined effect of body size, coloration, radiation, and air current in medium-sized insects was studied, and the results show that the excess temperature varies with from 0.4 to 1.0 power of the body size, compared with 0.4 to 0.7 power in control experiments with spherical plasticine models (4). As regards poikilothermic animals in general, several good reviews are available (see 5, 6, 7, 18).

The specific heat of the sickle-shaped human erythrocyte was found to be normal, so the condition cannot therefore be attributed to abnormal crystallization of haemoglobin. On the other hand, the specific heat of normal red cells decreases somewhat on slight heating (8).

Rate Processes

Temperature coefficients.—To describe the extent of the response to temperature variations of physiological rate processes, three kinds of temperature coefficient mainly are used, namely, Q_{10}, μ (otherwise written as E, or A), and b [in the b, α-rule (cf. 1)]. Most authors apply these constants merely as a means of description without accepting the theoretical implica-

[1] The survey of the literature pertaining to this review was completed in May, 1956.

tions attached to any one of them; for this purpose Q_{10} is still most widely used despite its recognized drawbacks, as it is the easiest to calculate. The somewhat more complicated *b*, α-rule, calculating the temperature from a specific zero point (α) upwards and using the log/log representation, has been recently applied by various authors to the reproduction rate of ciliates (9, 10); to the rate of respiration in bacteria (11, 12), sliced mammalian tissue (13), and insects (14); to the rate of movement in insects (15); and to the rate of development in trout (16) and batrachians (17). It was considered suitable for more general use in physiology (7, 18).

A linear relationship between rate and temperature was established in learning and forgetting processes in mollusks (19), in the respiration of arctic fishes (20), in the heartbeat of the excised heart of *Asellus* (21), etc. It should be noted that this relationship is merely a special case of the *b*, α-rule, where $b = 1$ and α lies close to 0°C., and the same is true of the rule of thermal sums, which can be converted into a linear relationship by using velocities instead of times (velocity = 1/time); the rule of thermal sums is widely used, especially by entomologists (7, 18).

Confirming and expanding certain earlier experiments in which it was found that the rate of haemolysis by sodium oleate was a function of temperature (1), Love (22), working with other detergents, e.g., sodium tetradecyl sulphate, has obtained "an amazing variety of results," expressed by unusually tortuous curves showing how complicated the thermic response can be in an apparently simple process; obviously no temperature coefficient can be computed.

Variation of temperature coefficients.—Contributions from various workers have added to the known instances of the considerable variability in magnitude of the temperature coefficient of one and the same physiological process with various factors. For instance, enhanced atmospheric pressure (4,000 lb./sq. in.) causes an increase in μ in the rhythm of frog myoblasts from the normal value of 18,500 cal. to 33,000 cal. (23), and in bacterial luminescence also the magnitude of μ is affected by increased pressure (26, 53). Osmotic variations of the water content modify Q_{10} and μ respectively in the respiratory rate of bacteria (11) and certain crustacea (24); and it has been confirmed that atmospheric humidity has an effect on the temperature coefficient of development in insects (25). Other agents affecting the numerical value of the temperature coefficient are the variations of pH in bacterial luminescence (26), the concentration of K ions in the heart beat of poikilotherms (27, 28) and in the electric potential of algal cells (29), the concentration of ethanol and some other narcotics in the respiration of rat brain tissue (30, 31), in insect respiration (32), in plant tissue respiration (33), and in the intensity of bacterial luminescence (26). Similar modifications of lesser or greater importance have been found in the temperature coefficients of the metabolic rate when the chemical nature of the substrate is altered in various protophyta (34 to 37) and protozoa (38).

In the respiration of the arctic stickleback age differences in the value

of Q_{10} have ben confirmed, lower values being encountered in younger individuals (39).

The analogous variations in response to the average temperature to which the organism is acclimatised are interesting. These variations in response are known in the rate of development of American batrachians from various latitudes (17), in respiratory exchange in fish (39), and in tissue respiration in fish (40). Homoiotherms and poikilotherms have been compared from this angle by Adolph (147).

As is known, the temperature coefficients of various physiological processes in a given organism may differ greatly in magnitude, and this point has been studied systematically in the frog (41, 42). Moreover, the various phases of a physiological activity may have temperature coefficients of different values. This has been demonstrated recently in the ascending and descending phases of the nerve action current (43, 44).

Injury of various kinds affecting, for example, the potential difference in frog skin (45), permeability in plant cells (46), anaerobic respiration in sea-urchin egg (47), and respiration in insects attacked by parasites (32), has been reported to affect the numerical value of Q_{10} (or μ) usually by lowering it. (It is to be noted that some previous work has demonstrated increased values of Q_{10} etc. in response to certain kinds of injury.)

The theory of "breaks."—This theory developed as a result of the use of the Arrhenius formula in physiology and the frequent finding of more than one value of μ for the temperature sector in question. Assuming that one and the same process can be regarded as based on several catalytic "master reactions" acting as pace-makers within certain ranges of temperature, it can now be abandoned. In addition to the objections raised previously (1), it has been pointed out that for a real "break" to be produced on the Arrhenius plot of a compound process, the rates of the pace-limiting processes in the two neighbouring temperature zones must have μ values differing from each other by at least 16,000 cal., whereas considerably smaller differences were usually claimed by supporters of this theory (45, 48 to 51). Objections have also been raised on the basis of a more detailed theoretical analysis of the ways in which cellular processes are mutually linked (18, 52). The topic has received detailed critical attention in the monograph by Johnson, Eyring & Polissar (53).

The artificial nature of the breaks is also evident from the application of the formula to the rate of enzyme reactions. Whereas oxidative enzymes as a rule give one single value of μ for the whole temperature range, hydrolytic enzymes usually give a value of μ that varies with the temperature in a way analogous to that found in cellular processes. The conclusion that, for example, splitting of maltose by a maltase would be based on more than one process would certainly be absurd. Moreover, a single value for b is found in most of such cases (54).

The theory of absolute rates.—The theory of absolute reaction rates has been postulated by Eyring (55) for chemical processes and applied by John-

son and his colleagues (53) to some biological processes. This theory is the outcome of statistical molecular mechanics which provide the basis of the kinetic considerations now prevailing in the theory of chemical change; as such it derives most of its theses from the temperature response of the reacting systems. Its central point is the concept of the "activated complex," an intermediary unstable molecule steadily formed by the reactants and then decomposed again, with a lifetime of about 10^{-13} sec. The frequency at which it decomposes is the same for all reactions and equals kT/h (k = Boltzman constant, T = temperature in absolute units, and h = Planck constant). It is thus possible to calculate the frequency of molecules reacting per second if their relevant properties are known. The equation devised for this purpose is a modified Arrhenius formula with 11 different constants; these express the enthalpy and entropy of the reaction, change in volume, action of pressure, effect of the steric configuration of the molecules, etc. For practical purposes and in ordinary conditions, the formula can be simplified and μ can be computed in the usual way, but with a modified theoretical meaning in view of its compound nature [in fact, it is supposed to consist of seven terms (cf. 53)].

The theory postulates that μ must vary with temperatures, for T figures as one of the seven terms, and another one, the entropy (S) is a temperature-dependent constant. Obviously there should be no "breaks" but a gradual change of μ with temperature. When μ is analysed some of the constants expressing the energy involved appear to be independent of temperature.

Johnson and his co-workers (26, 53, 214) have applied the theory particularly to bacterial processes, such as luminescence, growth, dehydrogenase activity, effect of inhibitors and disinfection, including inactivation by heat. The participation of pressure in determining the rate of such processes was examined and found to be in agreement with the theory.

Apart from the chemical change proper, the theory of absolute rates also embraces diffusion, solubility, and viscosity, and in fact any molecular rate process. In all of these processes the activiated complex is thought to determine the rate; for example, in diffusion a temporary combination between the molecules of the solvent and the solute, which affects the rate of the process, represents the activated complex (55).

However, important deviations (of 100 per cent or more) of the experimental rates from the theoretical values take place even in simple instances, for example, the diffusion of mannitol in water [cf. 55, (p. 623)]. In chemical processes the rates obtained theoretically may be in error by a factor of 10 to 100, or even more (56). It cannot be hoped that the theory will fit the physiological processes more precisely. This may set practical limits to the applicability of the theory of absolute reaction rates in physiology, apart from a selected number of relatively simple phenomena (67).

The role of diffusion.—The question as to the extent to which the velocity of physiological activities and its temperature coefficients are determined or co-determined, by the rate of diffusion of the reactants in the immediate

cellular environment, across the cell membrane and within the cell itself, has received continued attention. It has been suggested that the rate of diffusion of oxygen to the cell surface might be the factor limiting the rate of respiration of plant tissues (57), chick embryo tissues (58), and the tissues of the animal organism as a whole (51). In the special case of thermophilic bacteria which are characterized by a very high oxygen requirement, the supply of oxygen is probably responsible for the rate of reproduction, and the temperature coefficient of the latter is identical with that of respiration (59).

The rate of some enzyme reactions taking place *in vitro* can be increased by agitating the medium, thus proving that the rate of diffusion is the factor limiting the rate of the chemical change (60). A theoretical case of "an enzyme inside a diffusion barrier" has been considered by applying the principles of molecular statistical mechanics, and the corresponding equations have been formulated (61). Protein monolayers have been proved to constitute a comparatively high energy-barrier even for the passage of water molecules (62). The importance of diffusion in living processes must be considered with relation to the general theory of steady state in life phenomena (63).

Although external diffusion need not in every case constitute a limiting factor, and its restrictive effect is frequently compensated by various physiological devices producing streaming of the respective solutions (64), the rate of intracellular diffusion is quite a different problem. The theory of absolute reaction rates eliminates this problem by assuming that an activated complex underlies the rate of diffusion in the same way as it does in chemical changes (65). Unfortunately, the rate of diffusion, even in water, is not described with sufficient accuracy by the formula proposed (see above).

A relatively high temperature coefficient in a physiological reaction cannot be regarded as proof that diffusion is not a restrictive factor. In general diffusion across thin films gives a high temperature coefficient, and the greater the energy barrier to be crossed by a diffusing substance, the higher the respective temperature coefficient will be (55, 65). Some biological processes in which diffusion is known to be a limiting factor may have unusually high temperature coefficients; such is the case in the encystment of the ciliate *Colpoda* in response to a diffusing yeast extract, where μ is about 46,000 cal./mol. [corresponding to a Q_{10} of 16.6 (cf. 66)].

Molecular resistance of protoplasm.—It has been pointed out (67) that the rate of cellular processes might be related to the resistance encountered in the various phases of the living substance by the reactants on their way to and from the place of reaction. In fact the entry of substances into a living cell is up to 3×10^6 times slower when compared with the rate of diffusion [or membrane diffusion (cf. 68)], and enzyme reactions take place up to 10^8 times more slowly inside the cell than outside (69, 70).

The *b*, α-rule was found suitable for expressing the effect of temperature

upon the viscosity of protoplasm and, moreover, to be identical with the equation proposed by Slotte in 1881 (251) for the temperature-viscosity relationship in various liquids, including water and aqueous solutions. In fact anything which takes place inside a cell takes place between hydrated particles. and consequently all kinds of molecular movement within living matter are associated with frictional resistance between water molecules, which are either free or attached to other molecules by various forces, chiefly hydrogen bridges. This resistance, varying from case to case, is thought to determine the real velocity of intracellular biochemical processes (67). The same relationship (the b, α-rule) was found to hold true for diffusion in water, electric conductivity of weak electrolytic solutions, and for certain hydrolytic enzyme reactions (54). Unlike as all these processes may appear, their common feature is the movement of hydrated molecules, or ions, along and against each other, and the frictional resistance between them. This theory is put forward as an alternative, though not as a contradiction, to the concepts based on the consideration of energy distribution among molecules, supposing that cellular kinetics is one of the phenomena which are accessible justifiably to more than one quantitative approach.

Identification of cytochemical mechanisms.—In view of the variability of the temperature coefficient of a given process with numerous factors, and of the criticisms raised against the theory of "master processes," no safe identification of the cytochemical mechanisms underlying physiological processes, merely by comparing their temperature coefficients, is possible. Nevertheless, identity of temperature coefficients can be regarded as sufficient to justify an experimental test. For instance, judged by its temperature coefficient, the duration of sleep induced by barbiturates appears to be determined by the rate of detoxication in the liver and of elimination by the kidney; experiment has proved this to be true (71).

On the other hand, different values for the temperature coefficients of two processes can be taken as proof that the underlying mechanisms are not identical, provided that the conditions are the same. For example, the slopes of the time-temperature curves in the learning and forgetting processes in certain mollusks are different (19), suggesting that the underlying mechanisms are unlike. Another example is provided by the Propazone-stable portion of the respiratory mechanism of the brain, the rate of which has it own characteristic temperature coefficient (30).

Photochemical reactions.—These reactions are easily identified by their very low Q_{10}. Bleaching of visual purple by visible light goes on at a practically unaltered rate at −79°C. (72), but bleaching in the dark or in infrared rays is correlated with a high temperature coefficient (73). Sensitivity towards x-rays is in general only slightly decreased in the cold (for bibliography see 74), but the damage can be reduced, or prevented altogether, if cold is applied after irradiation (75, 76, 77). Ovarian tissue of rats is less damaged if the x-irradiation takes place at −79°C. (78) than at room temperature, the corresponding Q_{10} being about 1.01. A relatively high

Q_{10} (1.28) results from experiments in which rats are exposed to lethal doses of x-rays at 14 to 15°C. and at 38°C. body temperature respectively (79). In seeds and pollen grains the effect of x-rays can be considerably lowered if the irradiation takes place at the temperature of liquid air (80). It has been pointed out that the sensitivity of chromosomes to x-rays depends on temperature to the same extent as does the formation of H_2O_2 on the x-irradiation of water (81). X-ray inactivation of phages gives a Q_{10} of 1.02 to 1.04, practically independent of the degree of their hydration (82). A high temperature coefficient occurs in the combined action of x-rays and heat, as for example in yeast cells irradiated at more than 45°C. (83).

Photodynamic action is known to behave with respect to temperature as a photochemical process. In erythrocytes, however, only the first phase of photodynamic lysis, involving an increase in permeability for cations, is independent of temperature (84).

As found by Kelner (85), microorganisms, moulds, and phages damaged by ultraviolet rays can be reactivated by visible light of ca. 5,100 Å wavelength; this "photoreactivation" is correlated with a relatively high temperature coefficient ([Q_{10}=3.0 in *Actinomyces* (cf. 85); and 1.86 to 8.3 in a phage (cf. 86)], suggesting the participation of a slow diffusion process.

Effect of Low Temperatures

Freezing and chilling.—The sharp line separating freezing, i.e., cooling with ice formation, from simple chilling without ice formation, can no longer be maintained. While the mechanical effects of the formation of ice upon the structure of the cell, or the osmotic effect of thawing can usually explain the damage caused by freezing, another cause of damage, especially when the process is reversible, is to be found in the chemical changes undergone by the protoplasm and its constituents under the mere thermochemical action of a low temperature, regardless of whether ice is formed or not. Thus "chilling" may occur at any temperature low enough to bring the cellular processes to a standstill; this may happen, for example, in certain reproductive functions of thermophilic parasitic worms at 30 to 35°C. (87) in the mammalian electroencephalogram at 18 to 20°C. (88), or in various tissues, including those of mammals and birds, on rapid refrigeration to the temperatures of liquid gases (89 to 93). The zone of tempeatures at which chilling phenomena occur is thus very extensive. When ice is formed, part of the effects of freezing may still be attributable to a thermochemical effect, and only part to the mechanical effect of ice formation, or dehydration on ice formation, or osmotic action on thawing.

In cryptograms adapted to frosty conditions and insect larvae living at very low temperatures in arctic regions, respiratory exchanges were found by Scholander *et al.* (20) to take place at temperatures as low as −38°C.; the curves of rate against temperature were regular and smooth, and the parts corresponding to temperatures above and below the zero point had a gentle slope, although the slope became steeper past the freezing point.

When decrease of the normal respiratory rate is taken as an index of the degree of damage caused to various tissues by too low a temperature after various lengths of exposure, as suggested by Fuhrman & Field (94), an exponential relationship between the length of exposure and the degree of damage can be established for low temperature both below or slightly above 0°C., and "reaction constants" of damage can be calculated; this points to a certain unity in the changes produced by low temperatures, irrespective of whether they lie below or above the zero point (95).

Supercooling.—The ability to assume the supercooled state is a frequent explanation of resistance to frost (41, 96), and the capillarity of the intercellular and intracellular spaces, which reduces the probability of the formation of crystallization centres, is assumed to be the main factor responsible for supercooling (98). Another important factor is the presence in the protoplasm of hydrophilic colloids which prevent free ice formation; present knowledge of this factor has been summarized by Luyet & Gehenio (91, 96). A formula connecting the lowering of the freezing point of water with the diameter of the capillary spaces has been tested on inorganic material; the freezing point can be depressed down to −32 or −43°C. (99). Lipman (100) has suggested that the resistance to frost of protoplasmic colloids is a result of the extremely fine capillarity. The frost resistance of organisms does not depend solely on their ability to undergo supercooling, as is stressed by Scholander *et al.* (20) in concluding their studies on arctic plants and animals.

Ice formation.—Luyet & Gehenio (92) measured thermoelectrically the temperature changes occurring in a myxomycete Plasmodium during the transfer from a supercooled condition to ice crystallization and further cooling; the plateau corresponding to the freezing temperature could be recorded. The microscopic picture of the process of ice formation was studied recently by Luyet & Gibbs (101) using plant material. The process affects the individual tissue cells in no regular order, but sudden "flash" crystallization of their contents appears haphazardly. Ice may form inside the cells before it forms in the intercellular spaces (102). Analogous studies by Bergh (103) show that, in muscle, ice masses form "fronts" proceeding either parallel to the fibres or perpendicular to them, according to the conditions. Ice formation and changes in the microscopic structure of a muscle subjected to freezing and thawing were described by Steiner (104).

The amount of water transformed into ice by freezing the tissues is a function of time and can be measured when the freezing is slow (105). It is also a function of temperature, the two states of water being in equilibrium with each other; at every given temperature a definite proportion of cellular water remains in the liquid state. This is why gradual dehydration occurs in tissues undergoing freezing.

Contrary to the widely accepted view, M. L. Harris (106) concludes that in certain instances recovery is possible after intracellular ice formation.

Frost resistance.—Scholander *et al.* (20) estimate by extrapolation that

an organism which can live for 10 days at 0°C. would be able to live longer than a million years at −42°C. Kapterev (107) reported what is probably the record survival time of an organism frozen in ice, namely, certain lower plants and a cladoceran brought back to life after being frozen in a deep ice layer in the tundra whose estimated age was one thousand years.

Resistance to temperatures well below the zero point has been confirmed for a number of organisms. Arctic lichens are capable of a perfect recovery after exposure at −183°C., if in a partly dehydrated state (20). Larvae of certain chironomids were found partly dehydrated within ice masses; they could be easily revived, and respiration was found at temperatures as low as −26°C. At −32°C. a droplet of dark, highly concentrated haemolymph in liquid state could be squeezed out of the otherwise frozen and brittle body. Recovery was still possible after subjection to such low temperatures (20).

Becquerel has extended his previous experiments on the survival at the temperatures of liquid gases of dry seeds, mosses, algae, pollen grains, tardigrades, etc.; he has reported a complete recovery of such organisms after an exposure to 0.05°K. (108, 109).

Also, fully hydrated tissues have been shown to withstand, with little or no injury, exposures at temperatures below their freezing point, or even at those of liquid gases. For instance, various tissues of the frog remain unaffected by several minutes' exposure at −100 to −160°C. (110) and mammalian tissues, including malignant tumours, can recover after exposure to −253°C. (111). The addition of certain substances, e.g., glycerol or ethylene glycol, seems to enhance considerably the frost resistance of mammalian tissues (93, 112). The effect is not osmotic, for sugar has no comparable protective power. Ovarian tissue plus added glycerol and exposed to −79°C. can still be successfully grafted (113). Glycerol imparts similar protection in the case of red cells also, and so do the amides and urea (114). Human sperm can survive for months at −78°C., and the survival is facilitated by glycerol (115, 116, 117).

The formerly established fact that some cells and tissues can withstand longer exposures at very low temperatures has been confirmed for ovarian tissue, which appears to survive longer at −190°C. than it does at −79°C. (118). Partial dehydration by simple evaporation increases the frost resistance of certain mammalian tissues (112). Among cellular particulates, isolated mitochondria can withstand freezing (119) and undergo only a slow reduction in activity; they are destroyed by slow thawing, however, and survive longer at 0°C. than at 2°C. (120).

Frost haemolysis.—Extensive work on frost injury has been performed on the red blood cell. Haemolysis need not occur in response to moderate frost if the speed of temperature changes around 0°C. is carefully controlled; the injury is then limited to an insignificant leakage of haemoglobin without haemolysis proper (121). Even at −78°C. the blood cells may remain "metabolically normal" and suitable for, for example, tranfusion, although

they gradually disappear with longer exposures (118, 122). Blood smears rewarmed after very rapid cooling to −190°C. show 77 per cent osmotically active erythrocytes, while slow cooling to the same temperature will destroy them through ice formation (89). Haemolysis takes place only after more than three-quarters of the water content of the blood has changed into ice. This point is reached at different temperatures in different lengths of time and regular curves are obtained when the degree of haemolysis, temperature, and time of exposure are mutually related (123). Ponder (124) has demonstrated that red cells undergo lysis after 12 hr. at −20°C., leaving behind colourless ghosts that differ from those found in other types of haemolysis, e.g., caused by digitonin, in that they do not fragment when heated to 50 or 60°C. Haemolysis produced by alumina is accelerated not only by warming up, but also by chilling and freezing, and is slowest at +4°C. (122).

Vitrification.—Luyet and his colleagues have continued their experiments on the possibility of survival of fully hydrated, or only partially dehydrated, cells and tissues rapidly cooled down to the temperatures of liquid gases; in such cases the living substance is thought to assume the solid state without ice formation, or the vitreous state (92, 125, 126). This view has now received support on mathematical grounds by applying the equation of Slotte for the temperature-viscosity relationship to data on the viscosity of protoplasm, and finding by extrapolation that the temperature for infinitely high viscosity occurs within the range of temperature at which the vitrification of protoplasm (and other viscous fluids) was observed (67). It is likely that the "biological zero point" of various physiological processes, which often lies considerably below 0°C. can be explained on the basis of amorphous solidification of protoplasm or of some of its phases.

Protoplasmic contraction.—The well-known shrinking of some cells and tissues at low temperatures, usually accompanied by the exudation of water, may result from the withdrawal of cellular water by the formation of extracellular ice, or may even occur without ice formation as a syneretic process. In plant tissues which survive at the temperatures of liquid gases the shrinking of protoplasm, hitherto thought to be attributable to plasmolysis, has been shown by Becquerel to be syneresis (109, 127).

Another type of protoplasmic contraction caused by cold is represented by the thermochemically produced shortening of muscle fibres as studied by Szent-Györgyi and his colleagues (128 to 133, 204, 205). The underlying process is a thermochemically induced association of myosin and actin; it can be reproduced with washed muscle and myosin (130). It may be that the frequently observed shrinking of various cells exposed to a low temperature is attributable to a similar mechanism. The rigor which develops in a muscle on thawing, and involves the loss of water, can be prevented by iodoacetate but not by KCN (134).

Chilling and chill injury.—Various new facts concerning this topic need not be discussed here except to refer to a special article in this volume by Kayser on hypothermia. The hypothetical explanation of the slowing down

or complete arrest of physiological processes by cold without ice formation, and of chill injuries now has to consider the possible participation of hydrogen bridges (67). This particular type of bondage, characterized by a relatively low energy content, is easily established and disrupted by temperature variation and together with other weak bonds is responsible for the changes occurring with temperature in the configuration of protein molecules, their hydration and attachment to other molecules, including protein complexes and also in enzymes. It has been suggested that the reversible inactivation of enzymes at low temperatures might be attributable to the very rigid "coiling" of their molecules, because of the increased strength and extent of their bonds (54, 135). In cases where cell activity is arrested by chilling at a temperature considerably higher than those at which enzymes are usually brought to a standstill, an analogous effect on the proteins and lipoproteins in the cell boundaries should be considered.

Effect of High Temperatures

Thermal optima and maxima.—In developmental processes the optima and maxima of the rates usually coincide with those at which development is normal; in psychrophilic species, however, they need not coincide, and in arctic fishes such as *Coregonus clupeiformis*, for example, the optimum for the rate of development is 9°C., but for normal development it is 2°C. (136). Entomologists now often refer to the "optimum" temperature as the temperature at which mortality during development is lowest (137).

The "subjective optimum" or "preferendum temperature" at which the individuals of a given species congregate when given the choice, does not always correspond to the "celerrimum" or optimum in the physiological sense but is usually slightly or considerably lower than the latter (138, 139). The preferendum temperature is not a sharp point on the temperature scale but rather a zone, owing to individual variability. This may be related to that encountered in thermal injury in insects (140).

Parasitic life may lead to a reduction in this ability, for instance, the gall acarid, *Sarcoptes scabiei*, which congregates at any temperature higher than 24°C., will easily pass into the range of temperatures where it is damaged by heat (141). In the body louse (*Pediculus vestimenti*) and the bed bug (*Cimex lectularius*), however, a well-defined preferendum is found viz., 31.3 to 32°C. and 38°C. respectively (138).

A selection of figures, partly new and partly recently confirmed or rectified, that may be of interest to the physiologist will be quoted. Striated muscle undergoes heat contraction on gradual heating at 47°C. in the frog and at 53°C. in the rabbit (132). The potential difference derived from single muscle fibres of *Rana pipiens* falls above 30°C. (142). Reversible heat paralysis of the whole animal occurs at 29°C. in *R. pipiens* (143), at 32°C. in *R. temporaria*, and at 39°C. in *R. esculenta* (144). The optimum temperature for the rate of normal development in American frogs is 23.6°C. in *R. sylvatica* (compared with 24°C. in the European *R. temporaria*), 28°C. in *R. pipiens*,

30°C. in *R. palustris*, 32°C. in *R. catesbiana*, and 35°C. in *R. clamitans* (17).

Oxygen consumption of the sliced ventricle of the rat's heart has an optimum of 37.5°C. (13, 147) whereas the corresponding temperature for liver tissue is 45°C. (146). Oxygen consumption of sliced brain tissue of the rat has an optimum of 40°C.; at 40.8°C. the rate begins to decelerate (145). Electroencephalogram in the rat ceases at 44 to 45°C. (88). Pulsating wing-veins in bats stop beating at 44 to 46°C. (148). The chemotropic activity of human leucocytes is at its highest between 37 and 40°C.; it is abolished at 55°C. (149).

The temperature at which the sensation of heat is transferred into that of pain has been assessed at 44.9°C. for human skin (150).

The time factor in the action of heat.—The relationship between the degree of heat damage and the time of exposure has been studied mainly in unicellular organisms, the number of individuals killed serving as a measure of the damage. Most of these experiments, conducted on various bacteria, show an exponential relationship; the number of killed cells in logarithmic terms directly inversely proportional to the length of exposure (6, 53, 151 to 154). The same relationship was found in viruses (155, 156). In certain protozoa the logarithmic phase is preceded by a short initial period of a relatively high death rate (157). The logarithmic order of the death rate in cellular populations is usually interpreted as being the result of a "first order" reaction or a unimolecular chemical process. Rahn (152) suggested that this relationship can be derived statistically from the principles of quantum biology, and it is valid only when death is taken as the criterion of injury; when other criteria are envisaged, for example partial damage only, the relationship is not necessarily simply exponential. The heat destruction of phages also follows the course of a first-order reaction (158). A non-exponential relationship has been found for heat injury in the sclerotia of myxomycetes (97). Orr (42, 159, 160) has compared heat-death curves in a number of different animals.

Rapid heating to a certain temperature is generally more injurious than slower heating (160, 161, 162), and the optimum temperature of development in *Amblystoma* is lower if the respective temperature is not kept constant, but fluctuates around an average (163).

The shortest recorded observable heat damage is probably that attributable to "flash heating," namely 0.45 sec. exposure at 68°C., survived by *Ascaris* ova (164; cf. also 3). The highest temperature used experimentally in biology is 400°C., which the spores of some bacteria have been stated to withstand for 20 to 30 sec. (165).

Temperature coefficients of heat injury.—In a number of instances the Q_{10} and μ respectively of the rate of heat damage have been determined. Their numerical values are, as a rule, high, for example, in various viruses (155, 156, 166, 167, 168), bacteria (6, 53, 153, 154, 169, 170), bacterial spores (165), certain seeds (171), protozoa (172), and insects (18, 173). In some cases more than one value for the temperature coefficient was found, for

instance in a coli-phage μ equals 14,000 cal. up to 65°C., and 137,000 cal. between 65° and 75°C. (168; cf. also 155).

Time-temperature combinations for a "minimum burn" in guinea pig skin are 49°C./5 min. and 51°C./1 min. (175); the corresponding Q_{10} is somewhat over 200. A remarkably low value of Q_{10} is characteristic of heat destruction of pollen grains, e.g., those of pine trees where $Q_{10}=3.2$ (176).

Heat and permeability.—Additional information has been produced on the great increase in permeability, and on the changes in semipermeability, at temperatures above the optimum. Osmotic haemolysis is facilitated in preheated chick erythroyctes, and the permeability to glycerol is increased (177). The escape of Na^+ which occurs in cat red cells near the optimum temperature is reminiscent of an enzyme reaction in its response to temperature (178), and the permeability of mammalian erythrocytes to HCO_3^- and to SO_4^- is much increased above the optimum (179). Increased loss of K^+ from red cells is observable at 50°C. (182) or even above 40°C. (186). In spite of the pronounced changes in permeability erythrocytes continue, even after a short exposure to 50°C., to be as good osmometers as usual (187). This finding was confirmed by Ponder (181), but the erythrocytes so treated showed increased osmotic fragility, and only a little more heating gave rise to a deterioration in their osmotic functioning. Also, red-cell fragments, obtained on heating to 48°C., are active as osmometers (180). Isotonic swelling of mammalian red cells is reduced as the temperature rises beyond 40°C. (186). Capillaries of the guinea pig acquire increased permeability for dyes between 45 and 52°C. following the development of erythema and preceding capillary stasis (175). Analogous changes of permeability on heating have also been described in the field of plant physiology (171, 188, 189). The cuticle of various insects becomes permeable to water above 35 to 60°C. (191, 192), and this also occurs in aquatic insects (190). The phenomenon is connected with the properties of the cuticular lipides and accompanying substances, and with their liberation from a loose combination with some other constituents.

Other cytological changes.—The supermicroscopic picture of bacterial cells damaged at moderately high temperatures is reminiscent of plasmolysis in higher plants; the cellular contents are clumped (193). The x-ray diffraction pattern of a frog nerve is upset at 58 to 61°C. (194).

Optical properties apart, protoplasmic viscosity increases above the optimum as confirmed for mosses (195) and algal cells (196). The change takes place before cellular death occurs. In measuring the speed at which the nucleolus becomes subject to the effect of gravity within the nucleus of an echinoderm oocyte, the viscosity of karyoplasm can be assessed; it decreases on warming within the normal temperature range and continues to do so above 30°C. in spite of definite structural changes that have taken place in the nucleus (197).

Structural changes preceding haemolysis in response to supraoptimal heating have been described in mammalian red cells. Rounding-up of the cell

contents, crenation of the contour, formation of pseudopodial protrusions, myelination of the surface and fragmentation are the first signs of heat injury (124, 180, 181, 183, 184, 187, 198). Red-cell ghosts, cast off by haemolyzing erythrocytes, one of the effects of, for example, digitonin, undergo similar fragmentation when heated to 49 to 54°C., depending on the amount of residual haemoglobin; the distance between the molecules of haemoglobin seems to be the determining factor in fragmentation (124, 184). Parallel to the microscopic changes, alterations of birefrigence and of x-ray spacing are observed in the red cells (199); antigenic material is discharged by them above 50°C. (185). At 50 to 60°C. a decreased oxygen uptake is noticeable in chick erythrocytes before heat death occurs in 30 to 60 min. (200). Glycolysis is reduced at 50 to 55°C., accompanied by leakage of lipoids to the extent of about 40 per cent (177, 201). The supermicroscopic picture of structural changes corresponding to the slightly supraoptimal temperatures is one of cell-surface destruction (202). The erythrocytes of the alligator show a decreased respiratory rate at 45 to 50°C. (200).

Frog muscle, fixed and microscopically examined after exposure to 37°C., shows fibrillar nodosities (203). Mammalian muscle in rigor caused by heating was examined by Steiner (104), with regard to its mechanical properties, by using special devices for the determination of viscosity; loss of water, to the extent of 40 per cent of total weight, was found to accompany the shrinking of muscular tissue on supraoptimal heating. Thermodynamic aspects of the heat contraction of vertebrate muscle were studied by Szent-Györgyi (204, 205) with regard to the properties of myosin and actomyosin. The contractile stalk of the Vorticellids, usually regarded as a simplified prototype of muscle, responds to exposure at supraoptimal temperatures by shortening, accompanied by loss of birefrigence (206).

The escape of histamine, together with histaminase and some other enzymes, was observed in mammalian lung, liver, and other tissues exposed at 42°C. (207, 208, 209).

Reversibility of heat injury.—Additional details of the reversible heat inhibition of physiological activities have been produced. Heat paralysis in European frogs develops at the same temperature at which oxygen uptake starts to diminish, namely at 32°C. in *R. temporaria* and at 39°C. in *R. esculenta* (144). In the former species, however, the lymphatic hearts have been stated to become paralyzed only at 39°C. (210). According to Seifriz (211), the cessation of protoplasmic streaming caused by heat in the myxomycete *Physarum* is reversible up to a temperature of 42°C.; paralysis can be obtained at 36°C. in 60 min., and at 40°C. in 3 min. The resulting Q_{10} is about 1,800. Reversible heat paralysis of the spermatozoa of the cock occurs at 50°C. in 1 to 2 min. (212). Electric potentials in the giant axon of the squid (*Loligo forbesi*) both at rest and in action, are reversibly abolished when 40°C. is reached (44).

Intensity of bacterial light reduced by moderate heat treatment can be reverted to normal by keeping the culture at a normal temperature (53,

213, 214). Similarly, biochemical changes produced in yeast cells at 47°C. can be partly reversed after several hours at a suitable temperature (215). Recovery is promoted by glycine and phenol (6, 216).

Paramecium sensitized to ultraviolet radiation by heat can be desensitized by keeping it at a lower temperature; with regard to nutritional requirements, recovery is conditioned by metabolism (217). Cellular division in some protozoa is brought to a stop at 35°C. but resumes its normal rhythm at 26°C. without delay (74). Moderate changes in the structure of red cells caused by heat, as revealed by the study of their crystalline properties, can be made reversible (199).

Specificity and non-specificity of heat injury.—It was often claimed in the past that the structural and physiological changes caused by heat can also be elicited by some other agents, and more recent information on this subject is available. Heat-induced structural changes, as revealed in bacteria under the electron microscope, do not differ from those caused by frost injury (193), and the differential resistance to heat in various bacterial species is similar to their resistance to certain poisons and narcotics and to variations in pH (218, 219); moreover, in bacteria, the order of death in heat destruction, namely the logarithmic order, is the same as in destruction by certain poisons (220). Instances of this kind are also known in higher plants (221) and animals; for example, identical aberrations of chick embryonic development can be brought about by heat, colchicine, and other related compounds (222). In the cat those brain cortex cells which are the most responsive to electric stimulation are at the same time most sensitive to damage by picrotoxin and by heat (223).

The current explanation is that the unstable condition characteristic of cellular life is easily transferred into the state of equilibrium characteristic of cellular death by the action of the most varied agents, and consequently that the transition from the one state to the other always occurs in more or less the same manner.

On closer inspection, however, differences do exist, especially in the damage produced by heat and that caused by low temperatures. Heat and frost coagulation of protoplasm differ in certain microscopic details; and in general recovery is more easily obtained after low temperature damage (101, 224). The same applies to biochemical changes of protoplasm and its components (225). Differences between various forms of haemolysis produced by heat, frost, or by saponin are evident from what has been said in the preceding paragraphs. Partial heat inactivation of bacteriophages can be completed by a subsequent exposure at 2°C. (226).

Heat resistance and external factors.—The general conclusion, connecting resistance to high temperatures with a low water content of protoplasm, has been derived mostly from the lower forms of life and has only a limited validity in higher plants and animals. It has been confirmed that protozoan cysts are more heat resistant than the active forms (227), as also are bacterial spores compared with active bacteria (165). Similarly in plants, the

embryo is more resistant to heat in dry seeds than it is on germination or after (171). The temperature coefficients of heat injury in the dehydrated forms of such organisms are not as high as in their respective hydrated forms [seeds (171)], and this also seems to apply to viruses (155).

Partial dehydration by osmosis imparts some degree of protection against excessive heat in certain bacteria (151), yeast cells (215), in various plant tissues (188, 195), and in the aquatic larvae of certain insects (228). On the other hand, the stalk of the Vorticellid ciliates develops heat contraction in salt solutions sooner than in fresh water (206).

There is a specific optimum environmental pH value for the survival of various cellular types at higher temperatures, and it usually coincides with the optimum pH for existence at normal temperatures [in bacteria (6, 26, 229, 230, 231, 250)]. Not only the rate of heat damage and survival times, but also their respective temperature coefficients, are modified by variations in pH.

Heat resistance of plant cells is modified in either direction by cations, in agreement with the lyotropic series; Li^+ decreases the resistance most, while Mg^{++} (as sulphate) imparts a certain protection (188). Increased concentration of K^+ reversibly lowers the optimum temperature for the heart impulse in the frog (232); the opposite effect is observed in the frequency of the heartbeat of the snail (27, 233). In the same species, partial substitution of NaCl by NaBr depresses the optimum temperature for heartbeat frequency (234). Heat resistance of mammalian nerve tissue, as shown by modifications of the bioelectric potential, depends on the concentration of K^+, both in motor and sympathetic fibres (235).

The contradictory results concerning the effect of various narcotics upon heat sensitivity, studied mostly in lower organisms, now seem to be clarified by postulating that the inhibitors fall into two classes, one increasing and the other decreasing the heat sensitivity (236). As far as bacteria are concerned, the first group is represented by ethanol (237) and urethan (26); the second by chlorbutanol (Chloretone) (236). In protozoa, however, chlorbutanol has the opposite effect [*Paramecium* (9)]. Carbamides can be arranged in a series in which their molecular size determines in what direction and to what extent the temperature optimum in luminescent bacteria is displaced (238). Temperature optima are lowered by heavy metals (237) and quinine (153, 154), whereas sugars shift them slightly upwards (151). Purines, cystein, and various vitamins seem to be without effect (215). Some substances, for example $HgCl_2$, depress the physiological activity without displacing the optimum (239, 240). Most of this work has been performed on bacteria and yeast.

Heat damage increases under high pressure (242, 243), but the opposite was found in certain bacteria in testing the theory of absolute rates (26, 53, 153, 154). Damage caused by ultraviolet or x-rays combines with that caused by heat; previous irradiation increases the heat sensitivity of protozoa (74, 217, 244) and of nucleoproteins studied *in vitro* (74).

Theory of heat injury.—Recent views on the molecular configuration of proteins and enzymes (see 245) have provided an incentive to speculations as to the nature of protoplasmic changes caused by high temperature. In this connection lipoproteins also have received close attention (245). The central interest, however, shifts to the more general topic of intramolecular and intermolecular bondages, in particular the hydrogen bridge (54, 67, 188, 247, 248, 249). The thermodynamic properties of the hydrogen bridge provide an explanation for the upper thermal limits of life; should life depend on the maintenance of a stronger bond, these limits would be higher, for instance, 400°C. in the case of the C — H bond (249). Apart from the hydrogen bridge, the S — H and S — S bonds are being studied (104, 245, 250).

Thermal Adaptation

Two instances of adaptation have been studied in particular, namely (*a*) adaptation on being transferred to a new temperature, and (*b*) adaptation of thermophilic bacteria.

When transferred to a new temperature lying within the normal zone a living system may after a certain (sometimes short) time undergo a steady change in the rate of its physiological activities, the change counteracting the original effects of the new temperature; the rates thus tend to be unaffected by temperature changes. Numerous examples have been demonstrated and collected by Precht *et al.* (6).

A new "dynamic" theory of the permanent adaptation to 80 to 90°C. in thermophilic bacteria has been put forward by Allen (59). It is not necessary for their cytoplasm to contain heat resistant enzymes: the high rate at which enzymes are destroyed by heat is compensated by the equally high rate of enzyme formation. This, of course, creates a new problem of the unusual thermal resistance of the mechanism of enzyme formation.

LITERATURE CITED

1. Bělehrádek, J., *Temperature and Living Matter* (Protoplasm Monographien **8,** Borntraeger, Berlin, Germany, 277 pp., 1935)
2. Chadwick, I. E., *Physiol. Zoöl.*, **12,** 151 (1939)
3. Kreezer, G. I. and Kreezer, E. H., *J. Cellular Comp. Physiol.*, **30,** 173 (1947)
4. Digby, P. S. B., *J. Exptl. Biol.*, **32,** 279 (1955)
5. Gunn, D. I., *Biol. Revs. Cambridge Phil. Soc.*, **17,** 293 (1942)
6. Precht, H., Christophersen, J., and Hensel H., *Temperatur und Leben* (Springer-Verlag, Berlin, Göttingen, Heidelberg, Germany, 514 pp., 1955)
7. Allee, W. C., Park, O., Emerson A. E., Park, T., and Schmidt, K. P., *Principles of Animal Ecology* (W. B. Saunders Co., Philadelphia, Penna., and London, England, 837 pp., 1949)
8. Ponder, E., *J. Gen. Physiol.*, **38,** 575 (1955)
9. Alpatov, V. V., *Bull. biol. méd. exptl. U.R.S.S.* **3,** 3(1937); *Bul. Mosk. Obšč. izpyt. prirody*, **44,** 221 (1935); *Ber. wiss. Biol.*, **37,** 57 (1936); **43,** 366 (1937)
10. Phelps, A., *J. Exptl. Zool.*, **102,** 277 (1946)
11. Ingram, M., *J. Gen. Physiol.*, **23,** 773 (1940)
12. Turner, A. W., and Legge, J. W., *Australian J. Biol. Sci.*, **7,** 479 (1954)
13. Fuhrman, G. J., Fuhrman, F. A., and Field, J., 2nd, *Am. J. Physiol.*, **163,** 642 (1950)
14. von Brand, T. *Biol Bull.* **84,** 148 (1943)
15. Chapman, R. F., *J. Exptl. Biol.*, **32,** 126 (1955)
16. Hayes, F. R., and Pelluet, D., *Can. J. Research*, [D] **23,** 7 (1945)
17. Moore, J. A., *Biol. Bull.*, **83,** 375 (1942)
18. Wigglesworth, V. B., *The Principles of Insect Physiology*, 4th ed. (E. P. Dutton & Co., Inc., New York, N. Y., 544 pp., 1950)
19. Piéron, H., *Compt. rend. soc. biol.*, **135,** 631 (1941)
20. Scholander, P. F., Flagg, W., Hock, R. I., and Irving, I., *J. Cellular Comp. Physiol.*, **42,** Suppl. I, 1 (1953)
21. Needham, A. E., *Nature*, **173,** 272 (1954)
22. Love, I. H., *J. Cellular Comp. Physiol.*, **36,** 133 (1950)
23. Landau, J., and Marsland, D., *J. Cellular Comp. Physiol.*, **40,** 367 (1952)
24. Capraro, V., *Bol soc. Italiana biol. Sperim.*, **15,** 339 (1940)
25. Rey, P., *Compt. rend. soc. biol.*, **121,** 1271 (1936)
26. Johnson, F. H., Eyring, H., Steblay, R., Chaplin, H., Huber, C., and Gherardi, G., *J. Gen. Physiol.*, **28,** 463 (1945)
27. Bachrach, E., *Arch. sci. phys. et nat.* (*Genève*), **25,** 23 (1943)
28. Bachrach, E., *Arch. sci. phys. et nat.* (*Genève*), **26,** 37 (1944)
29. Blinks, L. R., *J. Gen. Physiol.*, **25,** 905 (1942)
30. Fuhrman, F. A., and Field, J., 2nd, *J. Cellular Comp. Physiol.*, **19,** 351 (1942)
31. Fuhrman, F. A., and Field, J., 2nd, *Proc. Soc. Exptl. Biol. Med.*, **69,** 331 (1948)
32. Payne, N. M., *Biol. Bull.*, **73,** 147 (1937)
33. Bottelier, H. P., *Rec. trav. bot. nëerl.*, **36,** 651 (1939)
34. Gould, B. S., and Sizer, J. W., *J. Biol. Chem.*, **124,** 269 (1938)
35. Tam. R. K., and Wilson, P. W., *J. Bacteriol.*, **41,** 529 (1941)
36. Johnson, F. H., and Lewin, I., *J. Cellular Comp. Physiol.*, **28,** 1 (1946)
37. Gaughran, E. R. L., *J. Gen. Physiol.*, **32,** 313 (1949)

38. Schoenborn, H. W., *J. Exptl. Zool.*, **105**, 269 (1947)
39. Scholander, P. F., Flagg W., Walters W., and Irving, I., *Physiol. Zoöl.*, **26**, 67 (1953)
40. Peiss, C. N., and Field, J., *Biol. Bull.*, **99**, 213 (1950)
41. Morales, M. F., *J. Gen. Physiol.*, **26**, 381 (1943)
42. Orr, P. R., *Biol. Bull.*, **91**, 232 (1946)
43. Finley, C. B., *J. Physiol. (London)*, **96**, 225 (1939)
44. Hodgkin, A. L., and Katz, B., *J. Physiol. (London)*, **109**, 240 (1949)
45. Barnes, T. C., *Physiol. Zoöl.*, **13**, 82 (1940)
46. Wartiovaara, V., *Ann. Botan. Soc. Zool.-Botan. Fenn. Vanamo*, **16**, 1 (1942)
47. Lindahl, P. E., and Sundin, J., *Nature*, **163**, 326 (1949)
48. Burton, A. C., *J. Cellular Comp. Physiol.*, **9**, 1 (1937)
49. Booj, H. L., and Wolverkamp, H. P., *Bibl. Biotheoretica*, **1**, 145 (1944)
50. Wolverkamp, H. P., and Booj, H. L., *Actualités biochim.*, **13**, (1949)
51. Morales, M. F., *J. Cellular Comp. Physiol.*, **30**, 303 (1947)
52. Monod, J., *Recherches sur la croissance des cultures bactériennes* (Actualités Scientifique et Industrielles, No. 911, Hermann & Cie., Paris, France, 210 pp., 1942)
53. Johnson, F. H., Eyring, H., and Polissar, M. J., *The Kinetic Basis of Molecular Biology* (John Wiley & Sons, Inc., New York N. Y. and Chapman & Hall, Ltd, London, England, 874 pp., 1954)
54. Bělehrádek, J., *Nature*, **173**, 70 (1954)
55. Glasstone, S., Laidler, K. J., and Eyring, H., *The Theory of Rate Processes* (McGraw-Hill Book Co., Inc., New York, N. Y., 611 pp., 1941)
56. Hougen, O. A., and Watson, K. M., *Chemical Process Principles* (John Wiley & Sons, Inc., New York, N. Y., 1107 pp., 1947)
57. Wanner, H., *Helv. Chim. Acta*, **28**, 25 (1945)
58. Philips, F. S., *J. Exptl. Zool.*, **86**, 257 (1941)
59. Allen, M. B., *Bacterial Revs.*, **17**, 125 (1930)
60. Schoenhyder, F., and Volquartz, K., *Biochim. et Biophys. Acta*, **9**, 306 (1952)
61. Best, J. B., *J. Cellular Comp. Physiol.*, **46**, 1 (1955)
62. Langmuir, I., and Schaefer, V. J., *J. Franklin Inst.*, **235**, 119 (1943)
63. Spanner, D. C., *Nature*, **172**, 1094 (1953)
64. Jacobs, M. H., *Ergeb. Biol.*, **12**, 1 (1935)
65. Danielli, J. F., and Davson, H., *J. Cellular Comp. Physiol.*, **5**, 495 (1935)
66. Brown, M. G., and Taylor, C. V., *J. Gen. Physiol.*, **21**, 475 (1937)
67. Bělehrádek, J., *Protoplasma* (In press)
68. Collander, R., *Protoplasma*, **33**, 215 (1939)
69. Barron, E. S. G., in *Biol. Symposia*, **10**, 27 (1943)
70. Barron, E. S. G., *Advances in Enzymol.*, **3**, 149 (1943)
71. Fuhrman, F. A., *Science*, **105**, 387 (1947)
72. Broda, E. F., and Goodeve, C. F., *Proc. Roy. Soc. (London)*, [B] **130**, 217 (1941)
73. St. George, R. C. C., *J. Gen. Physiol.*, **35**, 495 (1952)
74. Giese, A. C., *Quart. Rev. Biol.*, **22**, (4), 253 (1947)
75. Allen, M. B., Schjeide, O. A., and Hochwald, I. B., *J. Cellular Comp. Physiol.*, **38**, 69 (1951)
76. Cook, E. F., *Radiology*, **32**, 289 (1939)

77. Latarjet, R., *Compt. rend.* **217,** 186 (1943)
78. Parkes, A. S., *Nature*, **176,** 1216 (1955)
79. Hajdukovic, S., Herve, A., and Vidovic, V., *Experientia*, **10,** 343 (1954)
80. Rajevski, B., *Brit. J. Radiol.*, **25,** 550 (1952)
81. Fabergé, A. C., *Genetics*, **35,** 104 (1950)
82. Bachofer, C. S., *Science*, **117,** 280 (1953)
83. Wood, T. H., *Arch. Biochem. and Biophys.*, **52,** 157 (1954)
84. Joos, H., *Radiol. Clin.* **18,** 37 (1949)
85. Kelner, A., *J. Cellular Comp. Physiol.*, **39,** Suppl. I, 115 (1952)
86. Dulbecco, R., *J. Cellular Comp. Physiol.*, **39,** Suppl. I, 125 (1953)
87. Smyth, J. D., *J. Exptl. Biol.*, **29,** 304 (1952)
88. Ten Cate, J., Horsten, G. P. M., and Koopman, L. J., *Electroencephalog. and Clin. Neurophysiol.*, **1,** 231 (1949)
89. Luyet, B. J., *Biodynamica*, **6,** 217 (1947)
90. Luyet, B. J., and Thoennes, G., *Science*, **88,** 284 (1938)
91. Luyet, B. J., and Gehenio, P. M., *Life and Death at Low Temperatures* (Biodynamica, Normandy, Mo., 341 pp., 1940)
92. Luyet, B. J., and Gehenio, P. M., *Biodynamica*, **6,** 93 (1947)
93. Billingham, R. E., and Medawar, P. B., *J. Exptl. Biol.*, **29,** 452 (1952)
94. Fuhrman, F. A., and Field, J., 2nd, *Am. J. Physiol.*, **139,** 193 (1943)
95. Fuhrman, F. A., and Bělehrádek, J. (Unpublished data)
96. Luyet, B. J., and Gehenio, P. M., *Biodynamica*, **2,** No. 48 (1939)
97. Luyet, B. J., and Hodapp, E. I., *Protoplasma*, **30,** 254 (1938)
98. Goetz, A., and Goetz, S. S., *Biodynamica*, **2,** No. 43 (1938)
99. Puri, B. R., Sharma, L. R., and Lakhanpal, M. I., *J. Phys. Chem.*, **58,** 289 (1954)
100. Lipman, C. B., *Biodynamica*, **2,** No. 45 (1939)
101. Luyet, B. J., and Gibbs, M. C., *Biodynamica*, **1,** No. 25 (1937)
102. Bugaievsky, M. F., *Compt. rend. acad. sci. U.R.S.S.*, N. S., **22,** 131 (1939)
103. Bergh, F., *Dansk. Koeletekn. Forskinginstit.*, Publ. No. 9 (1948)
104. Steiner, G., in *Händbuch Kältetechnik*, **IX,** 313 (1951)
105. Luyet, B. J., and Condon, H. M., *Biodynamica*, **2,** No. 37 (1938)
106. Harris, R. J. C., *Biological Applications of Freezing and Drying* (Academic Press, Inc., New York, N. Y., 415 pp, 1954)
107. Kapterev, P., *Compt. rend. acad. sci. U.R.S.S.*, N.S., **3,** 137 (1936)
108. Becquerel, P. *Compt. rend.* **231,** 281 (1950)
109. Becquerel, P., *Compt. rend.* **232,** 22 (1951)
110. Sollman, T., Hoen, N. L., and Estable, J. J., *Am. J. Physiol.*, **156,** 333 (1949)
111. Klinke, J., *Growth*, **3,** 163 (1939)
112. Taylor, A. C., and Gerstber, R., *J. Cellular Comp., Physiol.*, **46,** 477 (1946)
113. Parkes, A. S., *Nature*, **176,** 1216 (1955)
114. Mollison, P. I., *Proc. Roy. Soc. Med.*, **47,** 64 (1954)
115. Shettler, L. B., *Am. J. Physiol.*, **128,** 408 (1940)
116. Polge, C., Smith, A. V., and Parkes, A. S. *Nature*, **164,** 666 (1949)
117. Bunge, R. G., and Sherman, J. K., *Nature*, **172,** 767 (1953)
118. Sloviter, H. A., *Nature*, **169,** 1013 (1952)
119. Loomis, W. F., *Arch. Biochem.*, **26,** 355 (1950)
120. Tager, J. M., *Nature*, **174,** 932 (1954)

121. Florio, M. S., and Mugrage, E. R., *J. Lab. Clin. Med.*, **28,** 1486 (1943)
122. Lovelock, J. E., *Nature*, **173,** 659 (1954)
123. Luyet, B. J., and Menz, L. J., *Biodynamica*, **7,** 25 (1951)
124. Ponder, E., *J. Exptl. Biol.*, **29,** 605 (1952)
125. Luyet, B. J., and Gomez, A., *Biodynamica*, **6,** 151 (1947)
126. Gonzales, F., and Luyet, B. J., *Biodynamica*, **7,** 1 (1950)
127. Becquerel, P., *Botaniste*, **34,** 57 (1949)
128. Hajdu, S., *Enzymologia*, **14,** 194 (1950)
129. Szent-Györgyi, A., *Enzymologia*, **14,** 177 (1950)
130. Szent-Györgyi, A., *Enzymologia*, **14,** 253 (1950)
131. Lajthe, A., *Enzymologia*, **14,** 255 (1950)
132. Hajdu, S., *Enzymologia*, **14,** 187 (1950)
133. Hajdu, S., and O'Sullivan, R. B., *Enzymologia*, **14,** 182 (1950)
134. Perry, S. V., *J. Gen. Physiol.*, **33,** 253 (1950)
135. Kavanau, J. L., *J. Gen. Physiol.*, **34,** 193 (1950)
136. Price, J. W., *J. Gen. Physiol.*, **23,** 449 (1940)
137. Grison, P., *Compt. rend. soc. biol.*, **141,** 1207 (1947)
138. Herter, K., *Z. Parasitenk.*, **12,** 552 (1942)
139. Falconer, D. C., *J. Exptl. Biol.*, **21,** 17 (1945)
140. Tsuchiyama, T., and Kosaka, K., *Bull. Ohara Agr. Inst.*, **36,** 277 (1944)
141. Mellanby, K., Johnson, C. G., Bartley, W. C., and Brown, P., *Bull. Entomol. Research*, **33,** 267 (1942)
142. Ling, G., and Woodbury, J. W., *J. Cellular Comp. Physiol.*, **34,** 407 (1949)
143. de Almeida, M. O., *J. Neurophysiol.*, **6,** 225 (1943)
144. Brachet, J., and Bremer, F., *Arch. intern. physiol.*, **51,** 195 (1941)
145. Field, J., 2nd, Fuhrman, F. A., and Martin, A. W., *J. Neurophysiol.* **7,** 117 (1944)
146. Fuhrman, F. A., and Field, J., 2nd, *Arch. Biochem.*, **6,** 337 (1945)
147. Adolph, E. F., *Am. J. Physiol.*, **166,** 92 (1951)
148. Mislin, H., *Rev. suisse zool.*, **48,** 563 (1941)
149. Fukushima, K., Senda, N., and Inui, H., *Med. J. Osaka Univ.*, **2,** 75 (1951)
150. Hardy, J. D., Goodwell, H., and Wolff, H., *Science*, **114,** 149 (1951)
151. Küster, E. (Doctoral thesis, Univ. of Erlangen, Erlangen, Germany, 1–45, 1939)
152. Rahn, O., *Biodynamica*, **4,** 81 (1943)
153. Johnson, F. H., and Lewin, I., *J. Cellular Comp. Physiol.*, **28,** 23 (1946)
154. Johnson, F. H., and Lewin, I., *J. Cellular Comp. Physiol.*, **28,** 47 (1946)
155. Price, J. W., *J. Gen. Physiol.*, **23,** 449 (1940
156. Lauffer, M. A., Carnelly, H. L., and MacDonald, E., *Arch. Biochem.*, **16, 321** (1948)
157. Loefer, J. B., and Mefferd, R. B., Jr., *Biol. Bull*, **103, 364** (1954)
158. Chang, S. L., Willmer, M., and Tegarden, L., *Am. J. Hyg.*, **52,** 194 (1950)
159. Orr, P. R., *Physiol. Zoöl.*, **28,** 267 (1955)
160. Orr, P. R., *Physiol. Zoöl.*, **28,** 294 (1955)
161. Rees, G., *J. Animal Ecol.*, **10,** 121 (1941)
162. Watanabe, Y., *Physiol. Zoöl.*, **23,** 258 (1950)
163. Mikulski, J. S., *Bull. intern. acad. polon. sci.*, [B] **1948,** 27 (1949)
164. Swales, W. E., and Froman, D. K., *Can. J. Research* [D] **17,** 169 (1939)
165. Oag, R. K., *J. Pathol. Bacteriol.*, **51,** 137 (1940)

166. Bloch, H., *Arch. Virusforsch.*, **2**, 288 (1942)
167. Cherry, W. B., and Watson, D. W., *J. Bacteriol.*, **58**, 601 (1949)
168. Bronson, L. H., and Parker, R. F., *J. Bacteriol.* **45**, 177 (1943)
169. Reuter, H., *Deut. tierärtzl. Wochschr.*, 87 (1948)
170. Pflug, I. J., and Esselen, W. B., *Food Technol.*, **7**, 237 (1953)
171. Siegel, S. M., *Botan. Gaz.*, **114**, 297 (1953)
172. Johnson, G., and Trussell, M. H., *Proc. Soc. Exptl. Biol. Med.*, **57**, 252 (1944)
173. Shull, A. F., *J. Explt. Zool.*, **89**, 183 (1942)
174. Pal, R., *J. Malaria Inst. India*, **5**, 77 (1943)
175. Sevitt, S., *Proc. Roy. Soc. Med.*, **47**, 225 (1954)
176. Hodgkins, E. J., *J. Forestry*, **50**, 450 (1952)
177. Hunter, F. R., and Pahigian, V., *J. Cellular Comp. Physiol.*, **15**, 387 (1940)
178. Davson, H., and Reiner, J. M., *J. Cellular Comp. Physiol.*, **20**, 325 (1942)
179. Luckner, H., *Pflügers Arch. ges. Physiol.* **250**, 303 (1948)
180. Ponder, E., *J. Gen. Physiol.*, **31**, 325 (1948)
181. Ponder, E., *J. Gen. Physiol.*, **32**, 391 (1949)
182. Ponder, E., *J. Exptl. Biol.*, **26**, 35 (1949)
183. Ponder, E., *J. Exptl. Biol.*, **27**, 191 (1950)
184. Ponder, E., *J. Exptl. Biol.*, **28**, 567 (1951)
185. Ponder, R., and Ponder, E., *Nature*, **170**, 928 (1952)
186. Fahraeus, R., *Acta Soc. Med. Upsaliensis*, **58**, 321 (1953)
187. Ham, T. H., Shen, S. C., Fleming, E. M., and Castle, W. B., *Blood*, **3**, 373 (1948)
188. Bogen, H. J., *Planta*, **36**, 298 (1948)
189. Belval, H., and Lemorgne, S., *Bull. soc. chim. biol.*, **29**, 667 (1947)
190. Marlier, G., *Ann. soc. roy. zool. Belg.*, **70**, 63 (1948)
191. Beament, J. W., *J. Exptl. Biol.*, **21**, 115 (1944)
192. Wigglesworth, V. B., *J. Exptl. Biol.*, **21**, 97 (1945)
193. Ruska, H., *Z. Hyg. Infektionskrankh.*, **123**, 294 (1941)
194. Elkes, J., and Finean, J. B., *Exptl. Cell. Research*, **4**, 69 (1953)
195. Schreibmair, G., *Protoplasma*, **29**, 399 (1937)
196. Northen, H. T., and Northen, R. T., *Plant Physiol.*, **14**, 175 (1939)
197. Harris, J. E., in Frey-Wyssling, A., *Deformation and Flow in Biological Systems*, p. 486 (North Holland Publ. Co., Amsterdam, The Netherlands, 552 pp., 1952)
198. Murphy, Q., *J. Cellular Comp. Physiol.*, **16**, 401 (1940)
199. Dervishian, in Ponder, E., *J. Gen. Physiol.*, **23**, 773 (1940)
200. Tipton, S. I., *J. Cellular Comp. Physiol.*, **3**, 31 (1933)
201. Hunter, F. R., and Stringer, I. D., *J. Cellular Comp. Physiol.*, **22**, 277 (1943)
202. Jung, F., *Klin. Wochschr.*, **21**, 917 (1942)
203. Carey, E. J., *Arch. Pathol.*, **30**, 881 (1940)
204. Szent-Györgyi, A., *Chemistry of Muscular Contraction*, 2nd ed. (Academic Press, Inc., New York, N. Y., 162 pp., 1951)
205. Szent-Györgyi, A., in *Modern Trends in Physiology and Biochemistry*, p. 377 (Barton, E. S. G., Ed., Academic Press, New York, N. Y., 538 pp., 1952)
206. Fauré-Fremiet, F., *Bull. soc. zool. France*, **66**, 277 (1941)
207. Kellaway, C. H., and Rawlinson, W. A., *Australian J. Exptl. Biol. Med.*, **22**, 63 (1944)

208. Kellaway, C. H., and Rawlinson, W. A., *Australian J. Exptl. Biol. Med.*, **22,** 83 (1944)
209. Rawlinson, W. A., and Kellaway, C. H., *Australian J. Exptl. Biol. Med.*, **22,** 69 (1944)
210. Hotovy, R., *Pflügers Arch. ges. Physiol.*, **242,** 180 (1939)
211. Seifriz, W., in Frey-Wyssling, A., *Deformation and Flow in Biological Systems*, p. 155 (North Holland Publ. Co., Amsterdam, The Netherlands, 552 pp., 1952)
212. Winberg, H., *Arkiv. Zool.*, [A] **33,** No. (7), 1 (1941)
213. Brown, D. E., Johnson, F. H., and Marsland, D. A., *J. Cellular Comp. Physiol.*, **20,** 151 (1942)
214. Johnson, F. H., Brown, D. E. S., and Marsland, D. A., *Science*, **95,** 200 (1942)
215. van Halteren, P., *Bull. soc. chim. Biol.*, **32,** 458 (1950)
216. Christophersen, J., and Precht, H., *Biol. Zentr.*, **71,** 313 (1952)
217. Giese, A. C., and Crossman, E. B., *J. Gen. Physiol.*, **29,** 79 (1945)
218. Baumgartner, J. C., and Knock, G. G., *J. Soc. Chem. Ind. (London)*, **59,** 53 (1940)
219. Johnson, F. H., and Gray, D. H., *J. Bacteriol.*, **68,** 675 (1949)
220. Rahn, O., *Bacteriol. Revs.*, **9,** 1 (1945)
221. Levitt, J., and Nelson, R. C., *Biodynamia.*, **4,** 57 (1942)
222. Ancel, P., and Lallemand, S., *Compt. rend. soc. biol.*, **13,** 221 (1941)
223. Teschan, P., and Gellhorn, E., *Am. J. Physiol.*, **159,** 1 (1949)
224. Sigenaga, M., *Cytologia*, **14,** 133 (1949)
225. Hagen, P. S., and Goas, M., *Compt. rend.*, **223,** 225 (1946)
226. Smith, I. S., and Krueger, A. P., *Proc. Soc. Exptl. Biol. Med.*, **81,** 254 (1952)
227. Taylor, C. V., and Strickeland, A. G. R., *Physiol. Zoöl.*, **9,** 15 (1936)
228. Hinton, H. E., *Trans. 9th Intern. Congr. Entomol.*, **1,** 478 (1952)
229. Beamer, P. R., and Tanner, F. W., *Zentr. Bakteriol. Parasitenk., Abt. II*, **100,** 81 (1939)
230. Beamer, P. R., and Tanner, F. W., *Zentr. Bakteriol. Parasitenk., Abt., II*, **100,** 202 (1939)
231. Johnson, F. H., and Lewin, I., *J. Microbiol. Serol.*, **12,** 177 (1947)
232. Benthe, H. F., *Z. vergleich. Physiol.*, **36,** 377 (1954)
233. Bachrach, E., and Guillot, N. G., *Compt. rend.*, **212,** 929 (1941)
234. Bachrach, E., and Reinberg, A., *Compt. rend. soc. biol.*, **145,** 870 (1951)
235. Lundberg, A., *Acta Physiol. Scand.*, **15,** Suppl. 50, 1 (1948)
236. McElroy, W. D., *J. Cellular Comp. Physiol.*, **21,** 95 (1943)
237. Lehotsky, P., *Arch. exptl. Zellforsch. Geivebezücht*, **24,** 359 (1942)
238. Johnson, F. H., Flagler, F. A., Simpson, R., and McGeer, K., *J. Cellular Comp. Physiol.*, **37,** 1 (1951)
239. Houck, C. R., *J. Cellular Comp. Physiol.*, **20,** 277 (1942)
240. Janisch, E., *Zentr. Bakteriol. Parastenk.*, **101,** 120 (1939)
241. White, R., Georgi, C. E., and Militzer, W. E., *Proc. Soc. Exptl. Biol. Med.*, **88,** 373 (1955)
242. Luyet, B., *Compt. rend. Soc. biol.*, **125,** 403 (1937)
243. Harvey, E. N., *J. Gen. Physiol.*, **25,** 855 (1942)
244. Giese, A. C., and Heath, H. D., *J. Gen. Physiol.*, **31,** 249 (1947)

245. Haurowitz, F., *Chemistry and Biochemistry of Proteins* (Academic Press, New York, N. Y., 374 pp., 1950)
246. Chargaff, E., *Advances in Protein Chem.*, **1**, 1 (1944)
247. Pauling, I., *The Nature of the Chemical Bond*, 2nd ed., p. 285 (Cornell University Press, Ithaca, N. Y., 450 pp., 1945)
248. Steinhardt, J., *Kgl. Danske Videnskab. Selskad., Biol. Medd.*, **14**, No. 2 (1937)
249. Lamanna, C., and Mellette, M. F., *Basic Bacteriology* (Williams and Wilkins, Baltimore, Md., 677 pp., 1953)
250. Anson, M. I., *Advances in Protein Chem.*, **2**, 361 (1945)
251. Slotte, K. F., *Weid. Ann. der Physik*, **14**, 13 (1881); *Beibl. Ann. d. Physik u. Chem.*, **16**, 182 (1892)

PHYSIOLOGICAL ASPECTS OF HYPOTHERMIA[1,2]

By Charles Kayser

Institut de Physiologie, Faculté de Medecine, Strasbourg, France

Definition of Hypothermia

Hypothermia designates a state in which an organism is at a lower temperature than in the normothermic state. As normothermia is achieved by a regulation, hypothermia is a disturbance of this regulation. The standard normothermia is that of the homeotherms. The temperature is set at a high level.

But there are other, less apparent normothermias, one of which is the normothermia of the hibernator: during winter sleep the temperature is set and regulated at a low level (620). Hibernal sleep will not be treated in this review.

Normothermia being the result of a regulation, it is clear that this state is not absolutely steady. There is, in the homeotherm, a thermal gradient from the central nucleus to the surface. This gradient is not constant. But even the temperature of the central nucleus undergoes "physiologic" fluctuations. One of the best known is the diurnal rhythm. Despite the fact that the temperature may oscillate by as much as 4°C. (323), it will not be considered here. The lowering of the central temperature is caused by an increase of the latent heat loss (442).

Physiologic and Accidental Hypothermias

Most of the physiologic hypothermias are not well known. Our knowledge exceeds only infrequently the level of the field naturalist's observation. The most surprising is the seasonal hypothermia of the bear (46, 194, 197, 436).

In primitive mammals, thermal instability and physiologic hypothermia have been known for a long time (195). Sometimes one has to distinguish between hypothermia and hibernal sleep in these species (199, 360). In the bat too, it is not easy to differentiate between the hypothermic state in summer and winter sleep (198, 338). Nevertheless in summer, the metabolic rate at all central temperatures is higher than in winter (342). The position of the bats among hibernators is becoming more and more difficult to define precisely (302, 499, 538, 551).

During "catastrophic" climatic conditions, birds can show accidental hypothermias (189, 321, 370, 403). Koskimies (366) thinks that, in the swift, this hypothermia can be considered as a true "adaptation." In contrast with these hypothermias is the winter sleep of the poorwill (325, 326). The mean

[1] This review includes a survey of the literature received in Strasbourg to June 1, 1956.

[2] My great thanks are due to my co-workers, Professors Marx and Metz, who translated this paper from the original French text.

weight loss of the poorwill during Jaeger's two month record was 2.4 mg. per kg. per 24 hr., which can be compared with the weight loss of the European ground squirrel in our investigations of a whole hibernating period which amounts to 2.5 mg. per kg. per 24 hr. (344). It can be concluded that the poorwill has a true winter sleep (327).

Transitory hypothermia is a natural occurrence in young birds and mammals which are immature at birth; many recent papers have been devoted to this already old problem (268, 476). This hypothermia can be considered as physiologic in so far as the mother, when building the nest, does not try to achieve an environment at thermal neutrality but at a lower temperature. Since their thermoregulation is deficient, when the mother leaves the nest, the young become hypothermic. This transitory hypothermia restrains neither the growth nor the development of the young animals (32 to 35, 196, 204, 211, 231, 233, 235, 239, 330, 452, 514, 520).

In all species in which hypothermia is physiologic, chemical thermoregulation is present and physical thermoregulation is either poor or lacking; it is the same as after shearing (448) or in hibernators during summer (339, 431). Hypothermia due to lack of chemical thermoregulation is very uncommon (166, 437).

Since the hibernal sleep state is a normothermic state set at a low temperature, the hibernator goes through a state of true hypothermia in autumn before falling asleep. He then shows very important thermal fluctuations, and his chemical thermoregulation regresses (229, 340, 410). This unstable state has not been much investigated. It occurs after the involution of the endocrine glands which are essential for thermogenesis and after the development of the hibernating gland (413). Sealander *et al.* (534 to 537) started a comparative investigation on the behaviour of a hibernator and some rodents under these conditions.

During winter sleep, hibernators periodically go again through such physiologic hypothermic states which constitute a transition between sleep and wakefulness. These transitory states have been investigated by many authors (7, 114, 116, 169, 354, 413, 416, 571, 572). It is a striking feature of the hibernator that when falling asleep, he lets himself cool down passively without shivering, while on the other hand, when waking he achieves a powerful heat production, in spite of a marked thyroid involution (489).

Hypothermia seems by definition to apply only to homeotherms. Nevertheless it must be pointed out that it applies also to poikilotherms; indeed they adapt themselves to their thermal environment. This means that the shift from one level to another breaks an equilibrium. In spite of the fact that the animal undergoes this shift passively, the metabolic rate following the van't Hoff-Arrhenius law, it remains true that poikilotherms adapt, i.e., change the oxidation rate when the environmental temperature is kept constant for a long time. This shows that the transition from one temperature to another constitutes a kind of "stress." Data concerning this problem can be found in the papers of Precht (494), Gelineo *et al.* (236, 237, 238) and Daw-

son & Bartholomew (170). Some time ago it had already appeared that the respiratory center of poikilotherms is less sensitive to small concentrations of CO_2 (up to 1 per cent) after lowering of the environmental temperature; correct ventilation at 5°C. is restored only after some time (341). Besides, the "adaptation" of the thyroid gland has been demonstrated for the first time in a poikilotherm (2).

General Reviews

The problem of hypothermia is now a major concern for surgeons (26, 57, 59, 138, 176, 177, 277, 286, 397, 502, 576, 616). Hypothermia now appears to be the best procedure enabling prolonged cardiac surgery. General reviews of this aspect of the problem have appeared from various laboratories for experimental surgery (63, 203, 404, 517, 602, 603).

Other workers have followed a different line of thought: since a release of histamine can be suspected in the postoperative disturbances (maladie postopératoire), shock, and many pathological disorders, they tried to achieve a moderate hypothermia (about 33°C. in man) by means of the combined action of a mixture of drugs (methonium salts, phenothiazine derivates, magnesium salts, curarizing drugs, barbiturates, etc.), which has been called, very inadequately, "artificial hibernation" (379, 384). The very name of this peculiar hypothermia and the speculations concerning its mechanisms, which were sometimes rather rash, gave rise to numerous disputes from which arose many general reviews on true hibernation, "artificial hibernation" and hypothermia (85, 124, 176, 177, 214, 216, 251, 252, 254, 255, 258, 334, 346, 347, 348, 517, 541). Surgeons, pediatricians, and pharmacologists have also held meetings concerning this subject (106, 136, 381, 451, 599).

In the publications from the Josiah Macy Foundation devoted to cold injury (135) many data concerning hypothermia may be found. In 1952 Talbott wrote a notable chapter on hypothermia (580). Burton & Edholm (87), as well as Precht, Christophersen & Hensel (495) have given many data on hypothermia in their books.

Methods for Producing Hypothermia

Giaja & Markovic-Giaja (259) distinguish primary and secondary hypothermias: in the first type, the heat production is reduced, as for example in hypothermia produced by hypoxia, by hypoxia and hypercapnia, by hypercapnia, by insulin, or by harmine, and that of hibernation; in the second, the heat loss is increased, as for example in *a frigore* hypothermia or after chlorpromazine. In animal experiments an extremely cold bath produces a hypothermia which supervenes so fast that the defense reactions which mark the stress are abolished (15).

In small animals the method of Giaja (248) is very often used and should be compared with the method of Ware *et al.* (612). Pichotka *et al.* (481, 482, 483) investigated very thoroughly the mechanism by which hypoxia produces hypothermia. Despite the valuable information which they can give,

surgical techniques are not used very often. These include large lesions in the hypothalamus or mesencephalon (504), cervical or thoracic cord transections (220), and cord destruction (122).

The methods for producing hypothermia in man can be classified in three groups (177). These techniques can also be used in animals weighing a few kilograms. The three groups are:

(*a*) External or surface cooling method, also called method of Fay & Smith (205, 554) and Swan *et al.* (577) including the use of various anesthetics (509).

(*b*) Internal methods of two different types: (*i*) the bloodstream cooling method of Boerema (72), Delorme (177), and Ross (517). The principle of this method was described in 1919 by Heymans (304). It has been recommended for intracardiac operations because it allows cooling without risks [to 25°C. in the dog (593)] and also a greater lowering of heart temperature. Cooling of the heart is achieved by extracorporeal circulation realized by various means (143, 176, 177, 273, 332, 335, 388, 394, 604). (*ii*) visceral cooling method with its own variants (68, 357, 474, 485, 518).

(*c*) Pharmacological artificial hibernation or method of Laborit & Huguenard (384).

Some of these methods require special equipment such as a pump (66, 332, 335), or heat exchanger (388), etc. To these methods should be added the methods of resuscitation by defibrillation of the heart (313, 393, 456) and by local warming of the heart (60, 167, 477).

Numerous drugs causing hypothermia have been described. Magnesium alone has not been used much (64, 295) but is a component of the drug mixture of Laborit & Huguenard. Harmine has been used (432). Among normal constituents of the organism there are histamine (287, 358, 418), lactic acid in the spinal animal (1), cortisone (337), and ACTH (184, 501). Epinephrine also can produce hypothermia (202, 257). Some authors attempted to imitate winter sleep and prepared extracts from brain (374), brown fat (613), and lymphoid tissue (465) in order to produce hypothermia. Insulin has been abandoned for a long time (103, 389) but is now used again associated with drugs having a central action such as chlorpromazine (305, 429, 471, 496, 506, 597).

Moderate hypothermias of central origin have been produced in decerebrate animals (279), by conditioning (549), by emotion (283) and by restraint (37, 38, 40, 41, 283, 303).

Hypothermia and Oxygen Intake

In homeothermic animals an increase in heat loss calls for an increase in heat production. But if heat loss becomes larger than heat production, the body becomes cooler. In homeothermic animals, the maximum heat production is observed in hypothermic states between 30 and 33°C. central body temperature in species ranging from mice to dogs; this is the "summit metabolism" of Giaja (247). The maximum amount of heat produced in this

state varies with several factors: duration of the cooling experiment, animal species, conditions of previous thermal adaptation (6,230, 234, 253, 258, 263). The summit metabolism, the maximum possible level of heat production, is limited by cardiac output according to Kramer & Reichel (369), while according to Giaja & Markovic-Giaja (260) its upper value depends on a fatigue of the cold receptors, since for the same animal oxygen consumption is higher at −10°C. than at 0°C. environmental temperature.

The increase of heat production during the first stage of hypothermia constitutes a stress involving the muscular performance of shivering as well as changes in the activity of many endocrine glands (215, 462, 484, 525, 563, 566, 610). The advocates of the mild pharmacological hypothermia (so called "artificial hibernation") believe that the many drugs used in that process reduce the reaction of the organism to cold stress (88, 89, 380).

When the critical point of the summit metabolism has once been passed, further decrease of the central body temperature leads to a decrease of the oxygen intake (4, 62, 120, 131, 179, 252, 348, 368, 378). At a body temperature of 20°C., one reaches another critical point: below this temperature spontaneous rewarming of the animal becomes impossible, while it is still possible when central body temperature remains above 20°C. At this temperature level, oxygen intake has approximately the value of the basal metabolic rate (258, 345). For body temperatures lower than 20°C., one can speak of "experimental poikilothermia" which is also called "pseudohibernation" by Kaminski (336). Since the respiratory quotient remains unaltered in this state (345), one can assume that the metabolic fuel is the same in hypothermia as in the normothermic state; some observed discrepancies (490) seem to be attributable to peculiar experimental conditions.

In many respects the oxygen intake during experimental hypothermia is similar to that of hibernating mammals during arousal; this also holds particularly for the values of the respiratory quotient (354) and for the validity of the surface law (263, 264, 354).

During experimental poikilothermic hypothermia, the basic features of heat production of both homeothermic and poikolothermic animals can be found (343). In homeotherms, the specific dynamic action of proteins amounts to 40 per cent at thermoneutrality. In poikilotherms (pythons), the heat increment amounts to more than 100 per cent (45) after food intake. Giaja & Popovic (265) have shown in the rat that the specific dynamic action of proteins, which amounts to 40 per cent before hypothermia, goes up to 150 per cent during deep hypothermia.

The metabolic heat production in hypothermia can be expected to depend passively on body temperature, according to the van't Hoff-Arrhenius rule. It can happen that the data obtained in hibernators during arousal (354) although apparently not showing this relationship, are still compatible with the rule. Spurr, Horvath *et al.* (317, 558) have made similar findings in the dog: the rule is still valid during shivering, with the exception that the general level of oxygen intake is higher than with no shivering. Bartlett *et al.*

(39) as well as Behmann (44) have also observed that the oxygen intake in hypothermia is related to the body temperature, according to the van't Hoff-Arrhenius rule.

The Lethal Temperature of Homeotherms in Hypothermia

Suspended animation.—Hypothermia is first of all a tool for experimental investigation: the physiologist calls on hypothermia in the same way as the chemist or the physicist does with temperature used as a factor of experimental analysis. By suppressing normothermia he is able to look into the different effects of temperature on the various functions of the body and to see whether the body passively undergoes reduction of its temperature or if some reactions appear.

Those physiologists who first were interested in hypothermia (53, 314, 315, 611) tried to find out why hibernating rodents were able to live for several months with central body temperature of about 5°C., while nonhibernating rodents could not survive when their central body temperature was reduced to 20°C. But the lethal level of the central body temperature is not known accurately: in the human species, reanimation of a woman whose temperature had fallen down to 18°C. (390) has even been reported. It has nevertheless been shown that the lethal temperature near 0°C. found in hibernating mammals was not a particular feature of winter sleep, but that it was also found in hibernators when cooled artificially. The lower lethal temperature of hibernators is therefore a feature of the hibernating species and not a seasonal feature connected with the state of hibernation (408).

The mechanism of hypothermic death remains rather unclear (453). In long lasting hypothermia experiments (557), death occurred in several ways: cessation of respiratory movements, fibrillation of the heart or cessation of the heart beat. Horvath (314) had already noted that the lethal temperature, defined as its level when the heart stops beating, was lower in dogs and rabbits when artificial respiration was used. According to Ruhe & Horn (519), death occurs from respiratory disturbances when the temperature of the brain falls to 16°C. In fact, cessation of respiratory activity is followed at a short interval by standstill of the heart (408). The temperature of cessation of breathing varies with the nature of anaesthetics used in inducing hypothermia (150, 601). The electrical activity of the brain disappears before breathing ceases (350).

But death as defined by standstill of the heart is only a superficial appearance, which has been called "Scheintod" by the German authors, or "suspended animation" (8, 13, 274, 408, 460, 461, 553). Actually rewarming allows resuscitation of hypothermic homeotherms whose heart has stopped beating, even if their body has been further cooled down to 5 or 6°C.

The tissues of homeothermic animals (rat, mouse) show respiratory exchanges in the Warburg apparatus to 5°C., sometimes even at lower temperatures. By plotting the logarithm of the oxygen consumption of tissues versus the reciprocal of the absolute temperature, a very regular straight-line rela-

tionship is found (555). Cold is used for the conservation of living tissues and tissue cultures (472, 473, 578). Low temperatures may even enhance the rate of proliferation of cancerous cells (310). Furthermore resuscitation of the hamster is still possible after cooling its body below 0°C., provided that crystallization of tissue water is avoided (553).

The possibility of resuscitating the whole body is limited in time: in rats definitive resuscitation is only possible if the state of suspended animation has not lasted over 60 to 70 minutes (9). The time of survival depends on the level of central temperature to which the animal has been cooled; by using the Giaja method of cooling (248) the periods of survival are 12 hours when rewarming from 15°C., 19 hours when rewarming from 18°C. and 29 hours when rewarming from 21°C. Similarly the duration of hypothermia compatible with resuscitation depends on the temperature level maintained during hypothermia: resuscitation is possible after keeping the animal hypothermic for 8 hours at 15°C. or for 13 hours at 18°C. This relationship seems to depend on a process which reaches an irreversible state progressively with increasing duration and lowering the level of hypothermia (557).

The possibility of resuscitation from the state of suspended animation, when the heart has been stopped by hypothermia, has an important practical bearing since it allows surgery on the heart made bloodless by occlusion of its circulation.

The critical temperature of standstill of the heart.—Newborn mammals exhibit a better tolerance to anoxia and hypothermia than do adult individuals (190). The critical temperature at which their heart stops beating is 10°C. lower than in adults of the same species (3). As shown by Adolph, young homeothermic mammals lose their ability to withstand anoxia before they do so for hypothermia. In adult rats Fregly (218, 219) found a negative correlation between the ability to withstand anoxia and the degree of adaptation to cold. In newborn guinea pigs the ability to withstand anoxia is connected with proneness to hypothermia (446, 447). In this species hypothermia enhances the ability to withstand all stresses and intoxications, as a direct effect of the reduction in energy metabolism (22, 249, 250, 262, 266, 288, 328, 414, 417, 433, 487, 565).

The proneness of newborn animals to hypothermia is most marked in the earlier stages of their postnatal development (5). According to Adolph, this could be the result of endocrine or nervous attributes undergoing changes during growth. While injections of growth stimulating extracts of the anterior pituitary did not reduce the critical temperature of standstill of the heart in adult rats (346), the total destruction of the nervous system allowed its reduction by about 2°C. in curarized rats (352).

Adaptation or acclimatization to cold by living for a time in a cold environment increases the ability to withstand more extreme cold exposures (27, 31, 69, 100, 201, 232, 234, 294, 324, 372, 373, 430, 533, 539, 540), but has no effect on the temperature of cessation of heart beat (4); nevertheless the oxygen intake during deep hypothermia is markedly increased (263, 267).

Mechanism of standstill of the heart in hypothermia.—The cessation of heart beat has been widely studied during experimental hypothermia, its mechanism arousing a strong interest since it is "the starting point of the events terminating in death" (298). When kept *in vitro* under artificial perfusion, the mammal heart stops beating at much lower temperatures than *in vivo* (5). One of the factors tending toward cessation of the heart beat is thus connected with *in situ* integrating conditions. No influence of the following factors has been found: somatotropic hormone (352), nervous system (349), epinephrine and norepinephrine (134, 349), vagus nerve (137). Cardiodynamic disturbances have been invoked since hypothermia increases the venous blood pressure (61). While Bigelow obtained a reduction of the lethal temperature following venous puncture, more recently Covino *et al.* (149, 150) could not find this effect. Edwards *et al.* (191) speak of a "partial loss of ability of the heart to convert aerobic energy into useful work." On the biochemical side, it was found that glycogen synthesis occurs in the rat heart kept at 16°C. (475) while the amounts of creatinephosphate or adenosinetriphosphate depend on the nature of anaesthetics used in inducing hypothermia (579).

The cardiac output was studied by Bigelow *et al.* (61). Hegnauer & D'Amato (296) reported that the output of the heart is reduced in a larger proportion than the total oxygen intake of the animal; the work of the heart is reduced from 2,625 gram-meters at 37°C. to 190 gram-meters at 17°C., but the reduction of the systolic output is not more than 50 per cent. The heart does not seem to undergo an undue stress at the lower temperatures, despite an increased blood viscosity (299). They suggest that "at some critical temperature or cardiac rate, because of the reduced coronary flow and the depressed rate of cellular oxidations, complete restitution fails between successive beats and a beginning metabolic debt develops." This explanation proceeds from the fact that, at body temperatures of 18°C., mechanical systole lasts for 70 per cent of the total duration of the cardiac cycle.

As noted by all investigators, fibrillation of the heart is the terminal event preceding death; fibrillation is the result of an abnormally high excitability of the myocardial fibers (577). Hegnauer and his team (148, 149, 151 to 154) have tried to provide experimental evidence of myocardial hyperexcitability. But more recently Hegnauer & Covino (297) have admitted that their experimental procedure was not adequate in this respect.

According to Harris *et al.* (292) potassium ions leave the intracellular space during hypothermia. According to Malméjac *et al.* (422) two processes bring the potassium out of the cells during anoxia: the action of epinephrine combined with a change in permeability of the membrane. Binet *et al.* (65) advocated injections of KCl with $CaCl_2$ to stop fibrillation. These facts suggest the possibility of abnormal depolarization and repolarization (282). The importance of coronary blood flow was noted by Hegnauer in 1950 (299) and later by Nahas *et al.* (454). Sabiston *et al.* (522, 523), and Badeer (23, 24)

found that the coronary blood flow in hypothermia was less reduced than the total cardiac output.

According to Gollan *et al.* (275, 276, 278), too large a coronary blood flow induced fibrillation; at very low body temperatures, the higher solubility of oxygen in blood improves the oxygen supply to the heart allowing a rather large reduction of coronary blood flow which helps to avoid fibrillation. Berne (54, 55) stresses the necessity of keeping the heart at a slow beating rate during hypothermia, owing to the interferences of cardiac contractions and coronary blood flow.

The variations of pH during hypothermia indicate a progressive acidosis which may displace potassium out of the cells and disturb the excitability of the heart (79, 80, 81, 152, 155, 212, 469, 575). According to Badeer (24) these phenomena have no connection with hypoxia. Hoff & Geddes (308), and Scherf *et al.* (529) have studied the functional alterations of the myocardium during hypothermia by carrying out localized cooling of particular areas of the heart.

Hypothermia and circulation.—The blood volume distribution changes with temperature (550). An extreme state is seen in the sleeping hibernator (400). But the most conspicuous action of temperature is seen on heart rate and arterial pressure. So, arterial pressure and the electrocardiogram have been studied in hypothermia as early as 1937 (157, 284, 290, 409). Nearly all general reviews on hypothermia devote an important chapter to these problems (61, 600). Whereas for Rodbard & Tolpin (513) there is in the chicken a parallel evolution of temperature, heart rate and arterial pressure, for most investigators, in the past as well as recently (128, 132, 291, 312, 455), the variation of arterial pressure differs from that of heart rate and temperature. This can be explained by the fact that the sinocarotid reflexes are still effective at 22°C. (186, 187); also the vasoconstrictive response to epinephrine is present at 16°C. in the rat (128). Even *in vitro* blood vessels are contracted by low temperatures (552). On the other hand, it seems that the action of, epinephrine on the heart rate is not the same at 37°C. and 16°C. (349, 375, 449). The slowing of the heart rate in cooling obeys closely the van't Hoff-Arrhenius rule (354, 439).

The biochemical analysis already made on the muscles of hibernators (208) has been started on the heart in hypothermia (579). The heart metabolism, especially during hypothermia, was studied by Bing (65a).

A great many papers are concerned with the action of temperature on the different waves of the electrocardiogram (84, 309, 398, 507, 528, 529, 545, 602). The investigations have been extended to primitive homeotherms (458) and hibernators (67, 168, 169, 306, 427, 524). Electric diastole undergoes the most marked lengthening by cold; conduction time and heart rate vary differently (351); the duration of the QRS wave and the ST interval are less affected by a lowering of the temperature.

These investigations have been complemented by many *in vitro* researches

(74): on the action of temperature on the mechanical properties of the heart (256, 307), and on the oxygen consumption of the myocardium (222, 555). The most important investigations which will give us information on the intimate action of temperature on the heart are the experiments performed with intracellular electrodes already started by Woodbury, Hecht & Christophersen (619), Trautwein, Gottstein & Federschmidt (589), Trautwein & Dudel (588), Heintzen (301), Coraboeuf & Weidmann (142), and Coraboeuf, Distel & Boistel (139).

Respiration and Body Fluids in Hypothermia

Hypothermic death was first related to the left-deviation of the oxyhemoglobin dissociation curve at low temperatures (408). This interpretation has not been given up (532, 615). However hypothermia brings on an acidosis which reduces or cancels this effect (81, 156, 212, 618) as was previously shown by Dill & Forbes (179). There are noticeable differences between hibernating mammals and hypothermic homeotherms in respect to their oxyhemoglobin dissociation curve (217) and their blood P_{CO_2}, pH and H_2CO_3 concentration (411, 413, 415). The hibernators exhibit also variations from summer to winter (438, 470).

The respiratory reflexes elicited from the chemoreceptors can still be found at 26°C. (459), but they are reduced and have only a small protective value during hypothermia. The vagal respiratory control disappears completely (36), one of the results of this being an increase of the physiological dead space (543).

By increasing the survival time of the nervous system after circulatory standstill, hypothermia allowed a study of the respiratory movements of gasping. Unlike urethane, cold depresses the two stages of gasping by simultaneous reduction of both aerobic and glycolytic cellular metabolism of the brain centers, according to Saathoff & Opitz (521).

The acidosis of hypothermia results from a decrease of OH ions of the body fluids (618) related to large variations of all ionic components of the blood plasma. Such variations were first investigated in the blood of hibernators; during winter sleep, plasma magnesium concentration is increased (508, 568). Suomalainen (568) related these variations to the sleeping state, but Metz & Mours-Laroche (443) could not find significant diurnal variations of plasma Mg in man, while the urinary output of Mg was significantly increased between 3 and 6 A.M. During experimental hypothermia, serum Mg is increased (486, 560, 567). In a comparative biochemical study, Platner & Hosko (486) showed that the relative variations of serum Mg (Mg concentration increase per °C. body temperature decrease) was the larger the lower the animal species in the series of vertebrates. Blood calcium also was first investigated during winter sleep (208, 464, 568) and later in experimental hypothermia (58, 133, 200, 404, 562). The various results are inconsistent both in winter sleep and in hypothermia. Quite a number of data are available on plasma potassium: as early as 1932 Ferdmann & Feinschmidt

(208) found a reduction in plasma K and this fact was confirmed by Suomalainen (569). In experimental hypothermia of homeotherms (58, 200, 376, 500), it was found that plasma K increases by diffusion of K out of the intracellular space (292, 293, 544). Nielsen (463) however noted a decrease of serum K in the hypothermic rabbit; similarly Fabian *et al.* (203) found a decrease of blood K in dogs in which shivering was restrained by chlorpromazine. A small and brief decrease of blood K was also observed by Lougheed *et al.* (404). Experiments on the lens of the eye (293), on the stellar nerve of *Loligo* (544), and on the rat diaphragm *in vitro* (97) have shown that cooling the cells directly influences the transfer of K through the membranes. While Brewer (78) had found in 1940 a correlation between metabolic activity and plasma K, it was shown more recently that various stresses (240) involve hormonal actions on the level of blood K, similar to the effects of cortisone and desoxycorticosteroids (20, 21, 505).

The variations of cation concentration in the extracellular fluid influence markedly the Donnan equilibria of the membranes and the excitability of nerve or muscle. Lundberg & Laget (406, 407) obtained such data for nerve fibers of various diameters. As related above, the same kind of phenomena may explain the fibrillation of the hypothermic heart (575). Fabian *et al.* (203) stress the possible role of an increase of the concentration ratio Ca/K for bringing on fibrillation of the heart.

The phosphate ion has been investigated during winter sleep (208, 464) as well as in hypothermia (562). Omachi *et al.* (468) followed the release of PO_4 by the isolated heart muscle at 37°C. and 26°C.; they found a temperature-rate relationship with a critical heat increment of 20,000.

The body fluid spaces were early studied by Barbour (30) who found that water enters the cells as long as the body reacts against hypothermia, while water leaves the cells when the body no longer reacts. D'Amato (159), D'Amato & Hegnauer (160), Horvath (316), as well as Morel & Combrisson (450), report similar findings. D'Amato related the entrance of water into the cells to shivering. Rodbard *et al.* (511, 512) advocate also partial peripheral circulatory occlusion in order to explain the water exchanges of hypothermia. By measuring the distribution space of P^{32}, Omachi *et al.* (468) could not find consistent variations of the extracellular space. The work of Meyer *et al.* (444) on the water and ionic equilibria in the goldfish verifies our previous assertion that in fish cold acts as a stress.

Nervous System

The words "cold narcosis" used for deep hypothermia in mammals indicated that this consequence of hypothermia on the functioning of the nervous system aroused a very early interest (547, 548). Thirty years ago Britton (82) made a thorough analysis of the progressive disappearance of reflexes. Fay & Smith (205) studied the effects of hypothermia in man. The same problem has been reinvestigated recently by Callaghan, *et al.* (98, 526).

Giaja (251), Popovic (488, 491), and Kayser (347) stressed the funda-

mental differences between sleeping hibernators and cooled homeotherms. In the first instance, the animals "react" to the most various stimuli, whereas in the second there is "cold narcosis." It seems unlikely that the special structure discovered by Chatfield & Lyman (115) in the floor of the fourth ventricle of the golden hamster is responsible for this difference. The great difference between the functional states of the encephalic centers in winter sleep and in artificial hypothermia is also revealed by central chronaxie measurements (123, 125, 126).

Hypothermia is well tolerated by the higher centers: using conditioned reflexes, Malméjac, Plane & Malméjac (427) showed that a central temperature 18°C. in the dog produced only transient disorders, and Andjus *et al.* (10) noticed that in the rat the lowest temperature which, after return to normal temperature, is compatible with learning, is 15°C. and that below this limit there is a significant impairment in problem-solving performance.

Since the work of Libet *et al.* (399), many papers (108, 209 for instance) still continue to be devoted to electroencephalographic studies of hypothermia. Electroencephalograms have been compared in winter sleep, arousal, and in experimental hypothermia (116, 119, 355, 412). Cortical activity can be registered down to 6°C. in hibernal sleep. Ransmeier & Gerard (503) found that in the golden hamster a temperature of 5°C. did not impair memory.

In cooled homeotherms the spontaneous electrical activity of the cortex disappears at 15 to 18°C. (350, 583). The mean frequency of the brain waves varies with the temperature according to the van't Hoff-Arrhenius rule in the homeotherm as well as in the poikilotherm (395, 396). Gänshirt *et al.* (224, 226, 227) investigated simultaneously the action of temperature on brain waves, oxygen consumption, and blood flow. In hypothermia the brain does not show any sign of suffering from hypoxia. These results are corroborated by the investigations of Rosomoff *et al.* (515, 516). Gänshirt *et al.* (227) also find slowing of the brain waves and a relative increase of slow waves. At 18°C. the electrical activity stops, preceded by a reduction of amplitude. Chardon (112) confirms these results. Koella & Ballin (361) find that the critical heat increment of the Dial bursts in hypothermia is 20,000 cal. The electroencephalogram during hypothermia produced by barbiturate anesthesia is not fundamentally different from the electroencephalogram during hypothermia produced by the so called "neuroplegic" drugs (285).

The primary cortical response to auditory stimuli (48, 362) is increased in hypothermia and spreads to the association areas. But on the other hand, the response to nociceptive stimuli is depressed (362). Koella & Ballin (362) concluded that the multineuronal path involved in arousal is very thermosensitive. Thus, hypothermia does not depress all central neuronic circuits in a uniform way.

Svorad (573, 574) investigating postural reflexes in progressive hypothermia, found that the cortical reflexes are abolished first, then the mesen-

cephalic, and last the bulbar. According to Chauchard & Mazoué (125), the mesencephalic centers still control the peripheral chronaxies in hypothermia.

The functioning of the vegetative centers has been investigated for a long time. Geiger (228) demonstrated that hyperglycemia in hypothermia is of central origin. The lungs of the cooled animal are markedly altered (421, 542). These alterations are seen only when the nervous system is present. Donnet *et al.* (182), Malméjac *et al.* (425), and Koella *et al.* (363) investigated vasomotor responses in hypothermia. In the dog at 25 to 29°C., Gellhorn (241) noticed a reduction of the adrenergic responses resulting from hypothalamic stimulation, whereas at the same temperature the action of acetylcholine and histamine were increased. Massopust (434) attempted to use hypothermia, combined with selective lesions in the hypothalamus, to determine the part played by the different hypothalamic nuclei in temperature regulation.

Hypothermia enabled Giorgio (269 to 272) to dissociate the cerebellar factor from the labyrinthine factor in the regulation of the tonus of the eye muscles. He investigated also the working of the respiratory center: in the guinea pig at 20°C. trigeminal reflexes could be elicited. According to Valerio & Carli (594), cold narcosis has the same action on the respiratory centers as ether anesthesia, while Saathoff & Opitz (521) consider hypothermia and urethane to act differently on the gasping center.

As to spinal centers, it follows from Brooks & Koizumi's studies (83, 364, 365) that moderate hypothermia increases their excitability. The monosynaptic response is followed by a late component; the activity of the interneurons is increased. Below 20°C. the opposite happens: excitability decreases and is abolished.

The physiology of peripheral nerve in hypothermia has also been often investigated. Chatfield, Lyman *et al.* (113, 117, 118) found fundamental differences in the resistance towards cold of the peripheral nerves of hibernators and homeotherms. They noticed too that a greater resistance to cold is linked with the peripheral anatomical situation of some nerves of homeotherms. In some species, such as the gull, adaptation to cold could be demonstrated. Douglas & Malcolm (183) studied comparatively the resistance to cold of A fibers (α, γ, δ) and C fibers. According to Stapel (559) and Chauchard (123) the chronaxies of peripheral nerves increase in the narcotized hypothermic animal. Experiments on frogs maintained at different temperatures showed that the regeneration of peripheral nerves was abolished below 8°C. (405). Krijgsman *et al.* (371) noticed that the same temperature did not have the same effect on the nerve of summer and winter frogs.

Kostial *et al.* (367), and Malméjac *et al.* (424) investigated the action of hypothermia on ganglionic transmission and on acetylcholine release. Tourpaev (587) found that in the frog the action of acetylcholine on the heart is maximal at 20°C. and decreases at higher and lower temperatures. He considers this fact as favoring the hypothesis that acetylcholine plays a part in an enzymatic reaction.

Endocrine Glands

Cold acts as a stress to homeothermic animals. Hematological and urinary evidence of this have been obtained recently by Mettinen (441), Kuhl *et al.* (377), Villalobos *et al.* (609), and Lavenda *et al.* (392). When initially cooled, the homeothermic animal calls upon all its thermoregulatory mechanisms, chemical as well as physical. If more heat is lost than is simultaneously produced, hypothermia sets in. Obviously all the signs of maximum thermoregulatory reaction can then be observed in light "secondary hypothermia" (260), including the responses of some endocrine glands.

Thyroid gland.—The fact that the thyroid gland is activated by cold exposure is without doubt. It is observed in poikilothermic (2, 467) as well as in homeothermic animals (14). Fontaine & Lachiver (215) published recently an important report on this problem. Thyroid activation begins early. There is a close correlation between oxygen intake and the morphological features of thyroid hyperactivity (14). When hypothermia has developed into "pseudohibernation" (14) those signs of thyroid hyperactivity disappear. Investigations with I^{131} confirmed the initial observations of Ariel & Warren (14). Verzar & Vidovic (605), Verzar *et al.* (606), Andjus *et al.* (11), and Aron *et al.* (19) have all noted a decreased uptake of I^{131} by the thyroid gland of animals in deep hypothermia. In hibernating species the same fact is observed during winter sleep (608). After adrenalectomy the animals no longer hibernate; the uptake of I^{131} then reaches the summer value (608). In this case also, the oxygen intake of the animal is proportional to the level of thyroid activity.

The control of thyroid activity has been studied by Beattie & Chambers (43). The uptake of I^{131} does not depend on the back-action of thyroxin on the release of thyrotropic hormone by the pituitary; the I^{131} uptake is also independent of the adrenal medulla. These conclusions agree with the results of Baldrick *et al.* (28) who found that I^{131} and P^{32} are taken up by the thyroid gland independently of the pituitary influences. Wher an effect of epinephrine is seen, a possible intervention of vasoconstriction is suggested.

Additional light is needed in this matter inasmuch as the earlier experiments of Turner & Turner (592) have not been challenged since 1940, when it was shown that the thyroid gland is activated by cold *in vitro*.

Adrenal medulla.—The role of the adrenals in hypothermia is far from being understood. The separate actions of the adrenal cortex and medulla are not always clearly differentiated. While the current view is that the adrenal cortex controls the ionic equilibria of the blood (401), the experiments of Tum Suden (590), Wener *et al.* (614), and Robertson & Peyser (510) show that epinephrine affects the partition of potassium between the various fluid spaces, possibly by peripheral circulatory restriction.

Even the role of the adrenal medulla on the control of heat production is rather complicated: according to some authors (202, 257, 556) epinephrine has no calorigenic action *stricto sensu*. On the other hand, Schaeffer & Thibault (527) have stressed the role played by epinephrine associated with

thyroxin. Finally, consideration must still be given to the classical observations of La Franca (387) and to the work of Cannon *et al.* (99).

The intervention of the adrenal medulla in thermoregulation and in hypothermia has to be considered in connection with its activation by the central nervous system: Maier *et al.* (421) could only avoid the pulmonary changes in hypothermia by combining adrenalectomy with total destruction of the nervous system. Malméjac *et al.* (424) have shown that the adrenal medulla is activated during hypothermia as long as the brain centers themselves are active, i.e., until 20°C. brain temperature. Cold has been shown to block peripheral synaptic transmission at approximately the same temperature. Fisher *et al.* (210) noticed that in the rat kept hypothermic at 20°C., the adrenal medulla no longer exhibits variations in its norepinephrine content and in the mass of its chromaffine tissue.

Laur (391) has paid attention to the hematological signs of stress: during hypothermia, with no stress as ascertained by the absence of tremor, urinary discharge and dyspnea, epinephrine will decrease the red cell count; the effect will be reversed if there is stress. Earlier experiments of Cassidy *et al.* (103, 104) had shown that epinephrine may revive shivering during hypothermia by means of its action on the blood sugar level.

Adrenal cortex.—Flückinger & Verzar (213) studied hypothermia while lowering barometric pressure. After a space of time, adaptation takes place and the central body temperature comes back to normal, but this can happen only if cortical hormone is available. Iampietro *et al.* (322) showed the protective action of the adrenals during hypothermia. Ganong *et al.* (223) found a reduction of 17-ketosteroid output and of adrenal blood flow during hypothermia.

According to a group of French authors (18, 89, 244) the action of cold exposure upon the adrenal cortex necessarily goes through an hypothalamico-pituitary-adrenal pathway, whereas Egdahl *et al.* (192, 193) and Beattie & Chambers (43) demonstrated that this effect was still obtainable after cutting the pituitary stalk and extirpating the pituitary gland. In fact, local cooling of the adrenals has the same effect on these glands as global body exposure to cold.

Pancreas.—It has been well known for sixty years that hibernating animals are hypoglycemic during their winter sleep (188). In this state there is an increase of the ratio of the β-cells to the α-cells in the pancreatic tissue (16). The fact that insulin simultaneously reduces the blood sugar level and the temperature of the body exposed to cold has also been well known for many years. Insulin stops shivering if the blood sugar level is sufficiently reduced (101, 102, 546). As early as 1925, Cassidy wrote of a "state simulating hibernation" when describing the effect of insulin. However the hyperglycemic action of epinephrine (70) is observed in hypothermia, when acute cooling leads its discharge (242, 359). Such an hyperglycemia does not appear after adrenalectomy.

When the body temperature is reduced to lower levels, hypoglycemia follows (87, 561). Popovic (493) followed the blood sugar level of the rat, cooled by hypercapnic anoxia, the temperature of which was kept at 17°C.; immediately after cooling the blood sugar was 300 mg. per 100 ml. blood. As hypothermia deepened, there was an exponential decrease; after six hours, the blood sugar fell to 100 mg. per 100 ml.; after 16 hours, it had fallen to 50 mg. per 100 ml. This low level was maintained by the hypothermic animal for twenty additional hours. Giaja *et al.* (261) report that death by hypoglycemia occurs at the same blood sugar level whatever the thermal state of the animal: normothermia with high or hypothermia with low energy expenditure. The hypoglycemic attacks do not appear at a definite critical ratio of blood sugar level to oxygen intake. In fact the attacks are more likely to be related to some direct effect of hypoglycemia on the nervous cells of the brain.

Genest (243) has done an histological investigation of both the endocrine and the exocrine structures of the pancreas in rats made hypothermic by drug action and killed after 4, 20, or 48 hours of hypothermia. During beginning hypothermia, the islets of Langerhans become undistinguishable from the exocrine structures; in a second stage, the exocrine structures exhibit cells with retracted protoplasm; in the last stage, i.e., after 24 hours, the cells are filled with secretory concretions.

Owing to the fact that in drug induced hypothermia, the body exhibits signs of stress such as hyperglycemia and tachycardia, Vegni & Prior (598) advocated the use of insulin for improving Laborit's drug-induced hypothermia (384), a rational advance proceeding from the thirty year old work of Cassidy (101, 102) and from the seventeen year old attempts of Suomalainen (568) to induce "artificial hibernation."

Gonads.—Vidovic (607) made the first studies of the effects of hypothermia on pregnancy in the female rat: after cooling by Giaja's procedure, an hypothermia at 15°C. was maintained once for four to eight hours; pregnancy was not disturbed in respect to its duration, to the size of the litter, nor to the weight of the newborn animals.

Courrier & Marois (145, 146) used the same procedure for repetitive cooling of pregnant female rats. If applied during the first days of pregnancy, hypothermia increases its duration. If applied after the eleventh day, repetitive hypothermia terminates pregnancy.

Pituitary.—Thibault (586) stressed ten years ago the important part played by the pituitary in the control of heat production. Hypophysectomized rats become hypothermic in environments below 35°C. Exposure at 20°C. makes their body temperature decrease to 31°C. Stone & Mason (564) indeed found that hypophysectomized rats build better nests, with higher thermal insulation.

Alimentary Tract

Digestion has not been much investigated in hypothermia. Gastric secretion is increased in a very cold bath when gastric temperature is already fall-

ing (435). An analysis of the mechanism of sugar absorption has been made by means of the action of temperature in poikilotherms (144). The rate of absorption of glucose, galactose, and fructose follows the van't Hoff-Arrhenius rule; the action of temperature on the absorption of xylose is less marked. This procedure confirmed the already ancient results of Cori concerning phosphorylation. Kerpel Fronius *et al.* (356) made similar studies on glucose and lipide absorption.

Kidney Function

In the hibernator *Citellus* the kidney still secretes at 5°C. (311). Secretion is extremely reduced; urinary concentration of phenol red is depressed but there is still reabsorption. In the rat, on the other hand, renal secretion can be studied only down to 16°C.; at this temperature, ingestion of water representing 4 per cent of the body weight gives a urinary output of 0.06 per cent of the body weight (311). Already at 30°C. the rate of secretion is markedly reduced, being only 25 per cent of the rate at 37°C. During the first stages of cooling there is a drastic transient reduction after which secretion is resumed but at a reduced rate.

The study of the action of temperature on the oxygen consumption of renal tissue slices (353) showed that the critical heat increment is different in the hibernator (*Citellus citellus, Cricetus auratus*) than in the homeotherm (rat, mouse). Kidney is the only tissue where such a significant difference could be observed. But if the hamster (*Cricetus cricetus*) is maintained awake in winter at 20°C. environmental temperature, the critical heat increment is then the same as in the rat or mouse.

In the hypothermic dog, oxygen consumption, blood plasma flow, and the clearance of creatinine and Umbradil (Diodrast) decrease when the temperature decreases (52, 333). After having been cooled down to 18 to 20°C., the kidney does not show any histologic lesions.

In the first stage of hypothermia the renal blood flow can increase (470), the maximum being reached between 38 and 34°C. In the second stage the renal blood flow decreases linearly with temperature by 8.24 per cent for each degree C. Filtration rate is less reduced, only 5.36 per cent per degree; the filtration fraction is therefore progressively increased. The extraction ratio of *p*-aminohippurate is unaffected by changes in rectal temperatures ranging from 38.2 to 27.5°C. T_m of *p*-aminohippurate is increased during shivering and subsequently decreases with temperature with a critical heat increment of 23,500 cal. Similar results have been reported by other investigators (445, 595). Nevertheless, according to Veghelyi & Harsing, electrolyte excretion is unchanged during hypothermia, or can even be increased. Na^{24} excretion is decreased at temperatures below 30°C. (12). The changes in sodium excretion seem independent of the action of the antidiuretic hormone. In man Talbott (580) noticed a reduction of the inulin, creatinine, and Diodrast clearances *pari passu* with the rectal temperature decrease until 34°C. In man too the filtration fraction is increased. During prolonged hypother-

mia, Popovic (493) reports that in the rat blood urea increases progressively from 48 mg. per cent to 70 mg. per cent when the rectal temperature is maintained at 15°C. for 14 hours. Prolonged hypothermia influences the production and excretion of urea differently. When an artificial kidney is used in the rabbit, Nielsen (463) no longer finds any changes in the blood potassium during hypothermia. Investigations on renal function in a poikilotherm such as the bullfrog (531) revealed that glomerular filtration and tubular reabsorption are reduced by cold whereas tubular secretion of urea is unaffected by this stress.

Artificial Hibernation or Moderate Pharmacological Hypothermia

General reviews.—Many general reviews discuss this problem (25, 47, 93, 109, 319, 384). In fact, artificial hibernation is a moderate pharmacological hypothermia in which sympathetic reactions are minimized (319). Laborit's artificial hibernation has many points in common with the hypothermias previously discussed; indeed it is only exceptionally that experimental hypothermia has been achieved without the action of drugs. On the other hand, however slight the hypothermia in pharmacological artificial hibernation, there is always hypothermia nevertheless.

Oxygen intake.—At first those who promoted this technique thought that cellular respiration was depressed irrespective of hypothermia. In fact, the oxygen need is determined by temperature: there is no reduction of metabolism without hypothermia (75, 76). The decrease of oxygen intake goes in parallel with the fall of temperature according to the van't Hoff-Arrhenius rule, just as in all other hypothermias where all temperature regulating reactions are abolished (62, 378). The curarizing drugs suppress shivering; chlorpromazine, by its adrenolytic and central actions, alters heat production slightly but increases heat loss markedly (49, 50, 109, 110, 120, 121, 206, 207, 289, 300, 492, 528, 581, 582, 617).

Nervous system.—Much criticism has been directed at the "so-called artificial hibernation methods" (280). This arose partly from the fact that the toxicity of the drugs used has not been sufficiently taken into account (140, 141, 147, 420, 426). Properties have also been attributed to the drugs which they do not actually possess (111, 180). Nevertheless the demonstration that chlorpromazine increases the resistance to a double stress, restraint and hypothermia, (419) remains valid.

Chlorpromazine has a general action on cells which is called "narcobiotic" (171, 172, 173, 185, 479, 480). This action is certain but the nervous system and more precisely some of its structures (reticular formation) are so much more sensitive that chlorpromazine is above all a drug acting on nervous centers (105, 127, 161, 162, 281, 305) even though metabolic actions on blood (158) or liver (42) can be demonstrated.

Many authors investigated the respiration of brain cells in the presence of chlorpromazine (29, 56, 225, 478). Cellular respiration is depressed, the nerv-

ous tissue appearing to be more sensitive than other tissues (478). Frowein *et al.* (221) did not find any histotoxic action in the isolated head.

The action of chlorpromazine alone or combined with hypothermia has been studied on vegetative centers: Dasgupta *et al.* (163, 164) on estrus and sham-rage; Donnet, Zwirn & Ardisson (181), Malméjac, Chardon & Neverre (423), and Dasgupta & Werner (165) on adrenosecretory and vasomotor centers.

Electroencephalography has been the subject of many papers: during sleep, the brain waves are slow (90, 96, 107, 584, 585) and the reaction to sensory stimulation is abolished or reduced (402, 591).

Huguenard & Fayot (320). and Laborit & Laborit (386) stress the usefulness of neuromuscular excitability measures in pharmacological hibernation, this being a simple procedure which could give information on ionic changes in the intra- and extra-cellular space.

Circulation, respiration, secretions.—Circulation has been the subject of numerous observations. Arterial pressure is increased at the beginning of ordinary hypothermia but this response can be partly suppressed by antihistaminic derivates of phenothiazine or by chlorpromazine (77). Dietmann (178) gave a full account of the action on circulation of 50 mg. of chlorpromazine in 20 subjects (measuring cardiac output, systolic volume, heart rate, etc). As in pure hypothermia, the venous pressure is increased in pharmacological hypothermia (73). The action of Hydergine and chlorpromazine on the right ventricular pressure has been investigated (95). The alterations of the electrocardiogram do not differ much from those in hypothermia (51, 92, 94, 95). Meriel *et al.* (440) measured the coronary and the renal blood flow. Frowein *et al.* (221) studied the cerebral blood flow in the chloralosed dog which also received chlorpromazine.

Malorny (428) compared arterial oxygen and carbon dioxide pressures in hypothermias induced in animals anesthetized with phenobarbital, urethane, or chlorpromazine. The ionic changes in the blood (fall of potassium, decrease of the ratio K/Ca) have been very often investigated (86, 174, 175, 382, 383, 385). Huggins *et al.* (318) studied the action of adrenolytic and histaminoloytic drugs on the toxicity of potassium chloride. Jaulmes *et al.* (329) followed the urinary elimination of the cations K, Na, Ca, and Mg. Noël, Cosnier & Genest (466) saw profound alterations in the exocrine and endocrine pancreas during the first hours of hypothermia; these regressed after 20 to 50 hours.

Endocrine glands.—The fundamental purpose of the pharmacological hibernation of Laborit was to abolish the reactions of the homeotherm to all aggressions (380); therefore those interested in this problem were led to investigations on the behavior of the adrenal and the thyroid glands during hypothermia in animals treated with the drugs used in the pharmacological hibernation method. In general the uptake of I^{131} by the thyroid is reduced (19, 71, 331). Aron *et al.* and Bobbio *et al.* attribute this effect to hypothermia.

As to the adrenal gland, both cortex and medulla have been investigated.

According to Aron (17), chlorpromazine produces a true pharmacological hypophysectomy. Most authors find only a reduction of the adrenal's reaction to stress (91, 129, 244, 245, 246) but the tests of the activity of the adrenal gland were not always the same (arterial blood pressure, blood sugar level, ascorbic acid, cholesterol, eosinophile count, reactions of ACTH injections). Since Vegni & Prior (496, 497, 498, 596) failed to find any reduction of the hyperglycemia in hypothermia, they advocated the use of insulin. It is well known that the blood glucose test is more sensitive than the blood pressure test for estimating the action of epinephrine (530).

Cheymol & Levassort (130) showed that hypothermic animals treated with chlorpromazine are more sensitive to hypoxia. It is also impossible to lower the critical temperature of heart standstill in curarized animals by the use of any one of the drugs composing the pharmacological mixture of Laborit-Huguenard (350). Despite the unquestionable toxic action of chlorpromazine (419, 420) there is surely a protection against stress but, as the experiments of Courrier & Marois (145) showed on the pregnant rat, thus protection is not general.

Most of the fundamental questions raised by hypothermia remain still unanswered. As long as only those investigating the mechanisms of life took an interest in the physiological problems of hypothermia, reports were sparse and our knowledge progressed slowly. Since hypothermia became a problem with immediate practical applications, the number of publications has increased enormously. But the legitimate hurry to succeed at any cost in solving the practical problem confronting surgeons and physicians has not increased, in the same proportion, as our insight in the physiological aspects of hypothermia.

LITERATURE CITED

1. Abenavoli, G., *Med. Sper.*, **23,** 611–26 (1953)
2. Adler, L., *Pflügers Arch. ges. Physiol.*, **183,** 23–39 (1920)
3. Adolph, E. F., *Am. J. Physiol.*, **155,** 366–77 (1948)
4. Adolph, E. F., *Am. J. Physiol.*, **161,** 359–73 (1950)
5. Adolph, E. F., *Am. J. Physiol.*, **166,** 75–91 (1951)
6. Adolph, E. F., and Lawrow, J. W., *Am. J. Physiol.*, **166,** 62–74 (1951)
7. Adolph, E. F., and Richmond, J., *J. Appl. Physiol.*, **8,** 48–58 (1955)
8. Andjus, R., *Compt. rend.*, **232,** 1591–93 (1951)
9. Andjus, R. K., *J. Physiol. (London)*, **128,** 547–56 (1955)
10. Andjus, R. K., Knöpfelmacher, F., Russell, R. W., and Smith, A. U., *Nature*, **176,** 1015–16 (1955)
11. Andjus, R., Lachiver, F., and Olivereau, M., *Compt. rend.*, **238,** 838–40 (1954)
12. Andjus, R., and Morel, F., *Compt. rend. soc. biol.*, **146,** 1477–81 (1952)
13. Andjus, R. K., and Smith, A. U., *J. Physiol. (London)*, **128,** 446–72 (1955)
14. Ariel, I., and Warren, S. L., *Cancer Research*, **3,** 454–63 (1943)
15. Armenio, S., and Sando, T. de, *Boll. soc. ital. biol. sper.*, **30,** 778–80 (1954)
16. Aron, C., and Kayser, C., *Compt. rend. soc. biol.*, **150,** 421–24 (1956)
17. Aron, E., *Anesthésie et analgésie*, **11,** 399–408 (1954)
18. Aron, E., *Rev. pathol. gén. et comparée*, **55,** 945–55 (1955)
19. Aron, E., Guelfi, J., and Voisin, A., *Compt. rend. soc. biol.*, **149,** 891–96 (1955)
20. Bachrach, E., *Arch. intern. Physiol.*, **54,** 19–29 (1946)
21. Bachrach, E., Reinberg, A., and Stolkowski, J., *Compt. rend. soc. biol.*, **147,** 651–53 (1953)
22. Baclesse, F., and Marois, M., *Compt. rend.*, **238,** 1926–28 (1954)
23. Badeer, H., *Am. J. Physiol.*, **183,** 119–20 (1955)
24. Badeer, H., *Circulation Research*, **3,** 8–31 (1955)
25. Badre, G., *Anesthésie et analgésie*, **11,** 53–61 (1954)
26. Bailey, C. P., Cookson, B. A., Downing, D. F., and Neptune, W. B., *J. Thoracic Surg.*, **27,** 73–91 (1954)
27. Baker, D. G., *Univ. Toronto Med. J.*, **29,** 285–87 (1952)
28. Baldrick, F. E., Brimblecombe, R. W., and Reiss, M., *J. Endocrinol.*, **12,** 205–8 (1955)
29. Balestieri, A., and Berti, T., *Boll. soc. ital. biol. sper.*, **29,** 1669–71 (1953)
30. Barbour, H. G., McKay, E. A., and Griffith, W. P., *Am. J. Physiol.*, **140,** 9–19 (1943)
31. Bargeton, D., *Arch. Sci. physiol.*, **9,** C47–C62 (1955)
32. Baric, J., *Bull. Acad. Serbe Sci.*, **12,** 3, (1953)
33. Barnett, S. A., and Manly, B. M., *Nature*, **173,** 355 (1954)
34. Bartholomew, G. A., Jr., and Dawson, W. R., *Ecology*, **35,** 466–72 (1954)
35. Bartholomew, G. A., Jr., Dawson, W. R., and O'Neill, E. J., *Ecology*, **34,** 554–60 (1953)
36. Bartlett, R. G., Jr., *Am. J. Physiol.*, **180,** 433–37 (1955)
37. Bartlett, R. G., Jr., Bohr, V. C., and Helmendach, R. H., *Proc. Soc. Exptl. Biol. Med.*, **86,** 395–96 (1954)
38. Bartlett, R. G., Jr., Bohr, V. C., Helmendach, R. H., Foster, G. L., and Miller, M. A., *Am. J. Physiol.*, **179,** 343–46 (1954)
39. Bartlett, R. G., Jr., Bohr, V. C., and Inman, W. I., *Can. J. Biochem. and Physiol.*, **33,** 654–57 (1955)

40. Bartlett, R. G., Jr., Helmendach, R. H., and Bohr, V. C., *Proc. Soc. Exptl. Biol. Med.*, **83**, 4–5 (1953)
41. Bartlett, R. G., Jr., Helmendach, R. H., and Inman, W. I., *Proc. Soc. Exptl. Biol. Med.*, **85**, 81–3 (1954)
42. Bartlett, R. G., and Register, N. D., *Proc. Soc. Exptl. Biol. Med.*, **90**, 500–2 (1955)
43. Beattie, J., and Chambers, R. D., *Quart. J. Exptl. Physiol.*, **38**, 241–48 (1953)
44. Behmann, F. W., *Arch. exptl. Pathol. Pharmakol.*, **228**, 126–28 (1956)
45. Benedict, F. G., *The Physiology of Large Reptiles*, 251–328 (Carnegie Institution of Washington, Washington, D. C., Publication No. 425, 539 pp., 1932)
46. Benedict, F. G., and Lee, R. C., *Hibernation and Marmot Physiology*, 227–229 (Carnegie Institution of Washington, Washington, D. C., Publication No. 497, 239 pp., 1938)
47. Benitte, A., *Arch. exptl. Pathol. Pharmakol.*, **222**, 20–41 (1954)
48. Benoit, O., Jouvet, M., and Tanche, M., *J. Physiol.* (Paris), **48**, 391–92 (1956)
49. Benstz, W., *Arch. exptl. Pathol. Pharmakol.*, **222**, 575–83 (1954)
50. Benstz, W., *Arch. exptl. Pathol. Pharmakol.*, **226**, 377–82 (1955)
51. Berendt, *Arch. exptl. Pathol. Pharmakol.*, **222**, 85 (1954)
52. Bergstrand, A., and Sterky, G., *Acta Physiol. Scand.*, **31**, 13–21 (1954)
53. Bernard, C., *Leçons sur la chaleur animale* (Baillière, Paris, France, 471 pp., 1876)
54. Berne, R. M., *Circulation Research*, **2**, 90–5 (1954)
55. Berne, R. M., *Circulation Research*, **2**, 236–42 (1954)
56. Berti, T., and Balestieri, A., *Boll. soc. ital. biol. sper.*, **29**, 632–34 (1953)
57. Bigelow, W. G., *Minnesota Med.*, **37**, 181–85 (1954)
58. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A., *Ann. Surg.*, **132**, 531–39 (1950)
59. Bigelow, W. G., Dolan, F. G., and Campbell, F. W., *The effect of hypothermia upon the risk of surgery* (Rapport XVIe Congrès International de Chirurgie, Copenhague, Imprimerie Médicale et Scientifique de Bruxelles, 14 pp., 1955).
60. Bigelow, W. G., Hopps, J. A., and Callaghan, J. C., *Can. J. Med. Sci.*, **30**, 185–93 (1952)
61. Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F., *Ann. Surg.*, **132**, 849–66 (1950)
62. Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F., *Am. J. Physiol.*, **160**, 125–37 (1950)
63. Bigelow, W. G., Mustard, W. T., and Evans, J. G., *J. Thoracic Surg.*, **28**, 463–80 (1954)
64. Binet, L., and Binet, P., *Bull. acad. natl. med.*, **138**, 395–403 (1954)
65. Binet, L., Strumza, M. V., and Strumza-Poutonnet, J. M., *Mém. acad. chir.*, (8–9), 277–78 (1951)
65a. Bing, R. J., *The Metabolism of the Heart*, 27–70, in *Harvey Lectures*, Series 50 (Academic Press, New York, N.Y., 421 pp., 1956).
66. Biörck, G., Damgaard-Nielsen, M., Haeger, K., Ryd, H., and Wulff, H. B., *Scand. J. Clin. Lab. Invest.*, **6**, 277–87 (1954)
67. Biörck, G., and Johansson, B., *Acta Physiol. Scand.*, **34**, 257–72 (1955)
68. Blades, B., and Pierpont, H. C., *Ann. Surg.*, **140**, 557–62 (1954)

69. Blair, J. R., and Dimitroff, J. M., *Am. J. Physiol.*, **171,** 709 (1952)
70. Blum, F., *Pflügers Arch. ges. Physiol.*, **90,** 716–29 (1902)
71. Bobbio, A., Goffrini, P., and Bezzi, E., *Presse méd.*, **60,** 1708–12 (1952)
72. Boerema, I. A., Wildschut, A., Schmidt, W. J. H., and Broekhuysen, L., *Arch. chir. néerl.*, **3,** 25–34 (1951)
73. Brancadoro, G., Ursini, M., and Alaimo, A., *Giorn. ital. Chir.*, **10,** 887–91 (1954)
74. Braveny, P., and Olesovsky, B., *Scripta Med. Fac. Med. Univ. (Brno and Olomounc)*, **28,** 221–28 (1955)
75. Brendel, W., Koppermann, E., and Thauer, R., *Pflügers Arch. ges. Physiol.* **259,** 177–206 (1954)
76. Brendel, W., and L'Allemand, H., *Arch. exptl. Pathol. Pharmakol.*, **225,** 87–90 (1955)
77. Breuninger, H., and Schmid, W., *Arch. exptl. Pathol. Pharmakol.*, **225,** 251–9 (1955)
78. Brewer, G., *Am. J. Physiol.*, **129,** 245–51 (1940)
79. Brewin, E. G., Gould, R. P., Nashat, F. S., and Neil, E., *Guy's Hosp. Repts.*, **104,** 177–214 (1955)
80. Brewin, E. G., Nashat, F. S., and Neil, E., *J. Physiol. (London)*, **127,** 19P–20P (1954)
81. Brewin, E. G., and Neil, E., *J. Physiol. (London)*, **126,** 26P (1954)
82. Britton, S. W., *Quart. J. Exptl. Physiol.*, **13,** 55–68 (1922)
83. Brooks, C. McC., Koizumi, K., and Malcolm, J. L., *J. Neurophysiol.*, **18,** 205–16 (1955)
84. Brooks, C. McC., Macfarlane, W. V., and Pinkston, J. O., *Am. J. Physiol.*, **171,** 711–12 (1952)
85. Brunaud, M., *Rev. pathol. gén. et comparée*, **55,** 892–914 (1955)
86. Buondonno, E., and Piro, S., *Acta neurologica*, **9,** 219–40 (1954)
87. Burton, A. C., and Edholm, O. G., *Man in Cold Environment*, 200–222 (E. Arnold Publisher, London, England, 273 pp., 1955)
88. Cahn, J., Dubrasquet, M., Georges, G., and Pierre, R., *Anesthésie et analgésie*, **10,** 397–408 (1953)
89. Cahn, J., Dubrasquet, M., Georges, G., and Pierre, R., *Anesthésie et analgésie*, **11,** 554–67 (1954)
90. Cahn, J., Dubrasquet, M., and Pierre, R., *Anesthésie et analgésie*, **11,** 358–73 (1954)
91. Cahn, J., and Georges, G., *Compt. rend. soc. biol.*, **149,** 1402–5 (1955)
92. Cahn, J., and Melon, J. M., *Anesthésie et analgésie*, **11,** 533–53 (1954)
93. Cahn, J., Melon, J. M., and Dubrasquet, M., *Thérapie*, **8,** 812–7 (1953)
94. Cahn, J., Melon, J. M., and Dubrasquet, M., *Compt. rend. soc. biol.*, **147,** 1193–96 (1953)
95. Cahn, J., Melon, J. M., Dubrasquet, M., and Bodiou, J., *Anesthésie et analgésie*, **11,** 513–32 (1954)
96. Cahn, J., and Pierre, R., *Anesthésie et analgésie*, **11,** 568–82 (1954)
97. Calkins, E., Taylor, I. M., and Hastings, A. B., *Am. J. Physiol.*, **177,** 211–8 (1954)
98. Callaghan, J. C., McQueen, D. A., Scott, J. W., and Bigelow, W. G., *Arch. Surg.*, **68,** 208–15 (1954)

99. Cannon, W. B., Querido, A., Britton, S. W., and Bright, E. M., *Am. J. Physiol.*, **79**, 466–506 (1917)
100. Carlson, L. D., Burns, H. L., Holmes, T. M., and Webb, P. P., *J. Appl. Physiol.*, **5**, 672–6 (1953)
101. Cassidy, G. J., Dworkin, S., and Finney, W. H., *Am. J. Physiol.*, **73**, 413–16 (1925)
102. Cassidy, G. J., Dworkin, S., and Finney, W. H., *Am. J. Physiol.*, **73**, 417–28 (1925)
103. Cassidy, G. J., Dworkin, S., and Finney, W. H., *Am. J. Physiol.*, **75**, 609–15 (1925/26)
104. Cassidy, G. J., Dworkin, S., and Finney, W. H., *Am. J. Physiol.*, **77**, 211–18 (1926)
105. Cathala, H. P., and Pocidalo, J. J., *Compt. rend. soc. biol.*, **146**, 1709–11 (1952)
106. Cathala, J., *Acta Paediat.* Suppl. 43, 211–8 (1954)
107. Cazzullo, C. L., and Guareschi, A., *Boll. soc. ital. biol. sper.*, **30**, 821–3 (1954)
108. Cazzullo, C. L., Guareschi, A., and Vitale, A., *Boll. soc. ital. biol. sper.*, **30**, 216–21 (1954)
109. Cerletti, A., and Fanchamps, A., *Schweiz. Med. Wochschr.*, **85**, 141–45 (1955)
110. Cerletti, A., and Rothlin, E., *Acta Neurovegetativa*, **11**, 260–74 (1955)
111. Chardon, G., *Compt. rend. soc. biol.*, **149**, 1539–41 (1955)
112. Chardon, G., *J. Physiol.*, **48**, 435–38 (1956)
113. Chatfield, P. O., Battista, A. F., Lyman, C. P., and Garcia, J. P., *Am. J. Physiol.*, **155**, 179–85 (1948)
114. Chatfield, P. O., and Lyman, C. P., *Am. J. Physiol.*, **163**, 565–74 (1950)
115. Chatfield, P. O., and Lyman, C. P., *J. Comp. Neurol.*, **101**, 225–35 (1954)
116. Chatfield, P. O., and Lyman, C. P., *Electroencephalog. Clin. Neurophysiol.*, **6**, 403–8 (1954)
117. Chatfield, P. O., and Lyman, C. P., *Am. J. Physiol.*, **177**, 183–86 (1954)
118. Chatfield, P. O., Lyman, C. P., and Irving, L., *Am. J. Physiol.*, **172**, 639–44 (1953)
119. Chatfield, P. O., Lyman, C. P., and Purpura, D. P., *Electroencephalog. Clin. Neurophysiol.*, **3**, 225–30 (1951)
120. Chatonnet, J., and Tanche, M., *Compt. rend. soc. biol.*, **149**, 716–19 (1955)
121. Chatonnet, J., and Tanche, M., *Compt. rend. soc. biol.*, **149**, 950–53 (1955)
122. Chatonnet, J., and Tanche, M., *J. Physiol.* (Paris), **48**, 439–42 (1956)
123. Chauchard, P., *Arch. intern. physiol.*, **63**, 153–60 (1955)
124. Chauchard, P., *Rev. questions sci.*, **16**, 254–67 (1955)
125. Chauchard, P., and Mazoué, H., *Compt. rend. soc. biol.*, **148**, 75–77 (1954)
126. Chauchard, P., and Mazoué, H., *Compt. rend. soc. biol.*, **148**, 883–84 (1954)
127. Chauchard, P., and Mazoué, H., *Compt. rend. soc. biol.*, **149**, 346–49 (1955)
128. Chevillard, L., Giono, H., and Popovic, V., *Compt. rend. soc. biol.*, **149**, 1925–28 (1955)
129. Cheymol, J., Leeuw, J. de, and Oger, J., *Compt. rend. soc. biol.*, **148**, 1213–16 (1954)
130. Cheymol, J., and Levassort, C., *Bull. soc. chim. Biol.*, **35**, 831–36 (1953)
131. Churchill-Davidson, H. C., Lynn, R. B., McMillan, I. K. R., and Melrose, D. G., *J. Physiol.* (*London*), **124**, 8P (1954)
132. Churchill-Davidson, H. C., McMillan, I. K. R., Melroe, D. G., and Lynn, R. B., *Lancet*, **265**, 1011–13 (1953)

133. Cier, J. F., Drevon, B., and Tanche, M., *J. Physiol. (Paris)*, **48,** 455–58 (1956)
134. Cier, J. F., and Tanche, M., *J. Physiol. (Paris)*, **46,** 299–300 (1954)
135. *Cold Injury. Trans. 1st Conf.* (Josiah Macy Foundation, New York, N. Y., 248 pp., 1952); *Trans. 2nd Conf.* (Josiah Macy Foundation, New York, N. Y., 242 pp., 1954); *Trans. 3rd Conf.* (Josiah Macy Foundation, New York, N. Y., 216 pp., 1955)
136. Colloque de Marseille. "Chirurgie intracardiaque expérimentale sous hibernation et hypothermie." *Anesthésie et analgésie*, **12,** 773–820 (1955)
137. Cookson, B. A., and Di Palma, J. R., *Am. J. Physiol.*, **182,** 447–53 (1955)
138. Cookson, B. A., Neptune, W., and Bailey, C. P., *J. Intern. Coll. Surgeons*, **18,** 685–94 (1952)
139. Coraboeuf, E., Distel, R., and Boistel, J., *Compt. rend.*, **240,** 2557–59 (1955)
140. Coraboeuf, E., Distel, R., Lavigne, S., and Boistel, J., *Compt. rend.*, **239,** 189–91 (1954)
141. Coraboeuf, E., Lavigne, S., Distel, R., and Boistel, J., *Compt. rend. soc. biol.*, **149,** 58–61 (1955)
142. Coraboeuf, E., and Weidmann, S., *Helv. Physiol. et Pharmacol. Acta*, **12,** 32–41 (1954)
143. Coraboeuf, E., Zacouto, F., Gaillard, R., and Saumont, R., *Compt. rend. soc. biol.*, **150,** 118–21 (1956)
144. Cordier, D., Maurice, A., and Chanel, J., *Compt. rend. soc. biol.*, **148,** 1417–18 (1954)
145. Courrier, R., and Marois, M., *Compt. rend. soc. biol.*, **147,** 1922–24 (1953)
146. Courrier, R., and Marois, M., *Ann. endocrinol.*, **15,** 738–45 (1954)
147. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P., *Arch. intern. pharmacodynamie*, **92,** 305–61 (1953)
148. Covino, B. G., and Charleson, D. A., *Am. J. Physiol.*, **179,** 627–28 (1954)
149. Covino, B. G., and Charleson, D. A., *Am. J. Physiol.*, **181,** 357–61 (1955)
150. Covino, B. G., Charleson, D. A., and D'Amato, H., *Am. J. Physiol.*, **178,** 148–54 (1954)
151. Covino, B. G., and Hegnauer, A. H., *Circulation Research*, **3,** 575–80 (1955)
152. Covino, B. G., and Hegnauer, A. H., *Am. J. Physiol.*, **181,** 553–58 (1955)
153. Covino, B. G., and Hegnauer, A. H., *Proc. Soc. Exptl. Biol. Med.*, **89,** 659–62 (1955)
154. Covino, B. G., and Williams, L., *Am. J. Physiol.*, **181,** 362–66 (1955)
155. Cranston, W. I., Pepper M. C., and Ross, D. N., *J. Physiol. (London)*, **125,** 20P–21P (1954)
156. Cranston, W. I., Pepper, M. C., and Ross, D. N., *J. Physiol. (London)*, **127,** 380–89 (1955)
157. Crismon, J. M., *Arch. Internal Med.*, **74,** 235–43 (1944)
158. Cruz, A. da, *Compt. rend. soc. biol.*, **149,** 1829–31 (1955)
159. D'Amato, H. E., *Am. J. Physiol.*, **178,** 143–47 (1954)
160. D'Amato, H. E., and Hegnauer, A. H., *Am. J. Physiol.*, **173,** 100–2 (1953)
161. Das, N. N., Dasgupta, S. R., and Werner, G., *Arch. intern. pharmacodynamie*, **99,** 451–57 (1954)
162. Das, N. N., Dasgupta, S. R., and Werner, G., *Arch. exptl. Pathol. Pharmakol.*, **224,** 248–52 (1955)
163. Dasgupta, S. R., and Häusler, H. F., *Arch. exptl. Pathol. Pharmakol.*, **228,** 188–89 (1956)

164. Dasgupta, S. R., Mukherjee, K. L., and Werner, G., *Arch. intern. pharmacodynamie*, **97**, 149–55 (1954)
165. Dasgupta, S. R., and Werner, G., *Brit. J. Pharmacol.*, **9**, 389–91 (1954)
166. Davis, T. R. A., and Mayer, J., *Am. J. Physiol.*, **177**, 222–26 (1954)
167. Davis, T. R. A., and Mayer, J., *Am. J. Physiol.*, **178**, 283–87 (1954)
168. Dawe, A. R., and Morrison, P. R., *Am. J. Physiol.*, **179**, 629 (1954)
169. Dawe, A. R., and Morrison, P. R., *Am. Heart J.*, **49**, 367–84 (1955)
170. Dawson, W. R., and Bartholomew, G. A., *Physiol. Zoöl.*, **29**, 40–51 (1956)
171. Decourt, P., *Compt. rend.*, **236**, 1195–97 (1953)
172. Decourt, P., *Thérapie*, **8**, 846–88 (1953)
173. Decourt, P., *Presse méd.*, **62**, 855–58 (1954)
174. Delga, J., Benitte, A., and Richard, S., *Compt. rend. soc. biol.*, **148**, 2012–14 (1954)
175. Delga, J., Benitte, A., Stupfel, M., and Richard, S., *Compt. rend. soc. biol.*, **148**, 260–62 (1954)
176. Delorme, E. J., *Acta Neurovegetativa*, **11**, 249–59 (1955)
177. Delorme, E. J., *British Med. Bull.*, **11**, 221–25 (1955)
178. Dietmann, K., *Arch. exptl. Pathol. Pharmakol.*, **222**, 60–63 (1954)
179. Dill, D. B., and Forbes, W. H., *Am. J. Physiol.*, **132**, 685–97 (1941)
180. Donnet, V., *Anesthésie et analgésie*, **12**, 817–20 (1955)
181. Donnet, V., Zwirn, P., and Ardisson, J. L., *Compt. rend. soc. biol.*, **149**, 377–78 (1955)
182. Donnet, V., Zwirn, P., and Ardisson, J. L., *Compt. rend. soc. biol.*, **149**, 754–55 (1955)
183. Douglas, W. W., and Malcolm, J. L., *J. Physiol. (London)*, **130**, 53–71 (1955)
184. Douglas, W. W., and Paton, W. D. M., *J. Physiol. (London)*, **117**, 2P (1952)
185. Driessens, J., *Compt. rend. soc. biol.*, **146**, 1186–87 (1952)
186. Dubecz, S., Kertai, P., Kokas, F., and Ludany, G., *Acta Physiol. Acad. Sci. Hung.*, **6**, Suppl. I, 83–4 (1954)
187. Dubecz, S., Kertai, P., Kokas, F., and Ludany, G., *Acta Physiol. Acad. Sci. Hung.*, **7**, 119–25 (1955)
188. Dubois, R., *Etude sur le mécanisme de la thermogenèse et du sommeil chez les Mammifères. Physiologie comparée de la Marmotte.* (Masson, Annales de l'Université de Lyon, Paris, 268 pp., 1896)
189. Dupond, C., *Gerfaut*, **27**, 226–27 (1937)
190. Edwards, W. F., *De l'influence des agens physiques sur la vie.* (Crochard, Paris, 654 pp., 1824)
191. Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A., and Bing, R. J., *Ann. Surg.*, **139**, 275–81 (1954)
192. Egdahl, R. H., Nelson, D. H., and Hume, D. M., *Science*, **121**, 506–7 (1955)
193. Egdahl, R. H., Nelson, D. H., and Hume, D. M., *Surg. Gynecol. Obstet.*, **101**, 715–20 (1955)
194. Egdahl, R. H., and Richards, J. B., *Memorandum Report 55-3 related to Project NM* 007 081.22. (Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md., 327–32 (1955)
195. Eisentraut, M., *Z. vergleich. Physiol.*, **16**, 39–47 (1932)
196. Eisentraut, M., *Mammalia*, **16**, 232–52 (1952)
197. Eisentraut, M., *Zool. Anz.*, **151**, 98–101 (1953)
198. Eisentraut, M., *Rev. suisse Zool.*, **60**, 411–26 (1953)

199. Eisentraut, M., *Mammalia*, **19**, 437–43 (1955)
200. Elliott, H. W., and Crismon, J. M., *Am. J. Physiol.*, **151**, 366–72 (1947)
201. Elsner, R. W., *Am. J. Physiol.*, **179**, 633 (1954)
202. Elvio, F., *Ormonologia*, **12**, 483–97 (1953)
203. Fabian, L. W., Stainton, R., Hara, M., Ling, P. C., and Shafer, C. W., *Current Researches Anesthesia & Analgesia*, **34**, 214–34 (1955)
204. Fairfield, J., *Am. J. Physiol.*, **155**, 355–65 (1948)
205. Fay, T., and Smith, G. W., *Arch. Neurol. Psychiat.*, **45**, 215–22 (1941)
206. Feller, K., *Arch. exptl. Pathol. Pharmakol.*, **225**, 90–1 (1955)
207. Feller, K., *Arch. exptl. Pathol. Pharmakol.*, **226**, 269–77 (1955)
208. Ferdmann, D., and Feinschmidt, O., *Ergeb. Biol.*, **8**, 1–74 (1932)
209. Ferrari, E., and Amantea, L., *Boll. soc. ital. biol. sper.*, **31**, 22–4 (1955)
210. Fisher, E. R., Fisher, B., and Fedor, E. J., *Proc. Soc. Exptl. Biol. Med.*, **89**, 140–42 (1955)
211. Fitzgerald, L. R., *Am. J. Physiol.*, **182**, 105–10 (1955)
212. Fleming, R., *Arch. Surg.*, **68**, 145–52 (1954)
213. Flückinger, E., and Verzár, F., *Helv. Physiol. et Pharmacol. Acta*, **10**, 349–59 (1952)
214. Fontaine, M., *Rev. pathol. gén. et comparée*, **52**, 53–64 (1953)
215. Fontaine, M., and Lachiver, F., *Arch. sci. physiol.*, **9**, C63–C81 (1955)
216. Fontaine, M., and Lachiver, F., *Rev. pathol. gén. et comparée*, **55**, 730–65 (1955)
217. Foreman, C. W., *J. Cellular Comp. Physiol.*, **44**, 421–29 (1954)
218. Fregly, M. J., *Am. J. Physiol.*, **176**, 267–74 (1954)
219. Fregly, M. J., *Am. J. Physiol.*, **176**, 275–81 (1954)
220. Freund, H., and Grafe, E., *Arch. exptl. Pathol. Pharmakol.*, **70**, 135–47 (1912)
221. Frowein, R. A., Hirsch, H., Kayser, D., and Krenkel, W., *Arch. exptl. Pathol. Pharmakol.*, **226**, 62–68 (1955)
222. Fuhrman, G. J., Fuhrman, F. A., and Field, J., *Am. J. Physiol.*, **163**, 642–47 (1950)
223. Ganong, W. F., Bernhard, W. F., and McMurrey, J. D., *Surgery*, **38**, 506–12 (1955)
224. Gänshirt, H., *Electroencephalog. Clin. Neurophysiol.*, **5**, 118–19 (1953)
225. Gänshirt, H., and Brilmayer, H., *Arch. intern. pharmacodynamie*, **98**, 467–74 (1954)
226. Gänshirt, H., Hirsch, H., Krenkel, W., Schneider, M., and Zylka, W., *Arch. exptl. Pathol. Pharmakol.*, **222**, 431–49 (1954)
227. Gänshirt, H., Krenkel, W., and Zylka, W., *Electroencephalog. Clin. Neurophysiol.*, **6**, 409–13 (1954)
228. Geiger, E., *Arch. exptl. Pathol. Pharmakol.*, **121**, 67–82 (1927)
229. Gelineo, S., *Compt. rend. soc. biol.*, **127**, 1360–61 (1938)
230. Gelineo, S., *Compt. rend. soc. biol.*, **147**, 134–36 (1953)
231. Gelineo, S., *Arhiv. Biol. Nauka*, **6**, 227–33 (1954)
232. Gelineo, S., *Compt. rend. soc. biol.*, **148**, 1114–16 (1954)
233. Gelineo, S., *Compt. rend. soc. biol.*, **148**, 1483–85 (1954)
234. Gelineo, S., *Arch. sci. physiol.*, **9**, 225–43 (1955)
235. Gelineo, S., and Gelineo, A., *Bull. Acad. Serbe Sci.* **4**, (2); *Sciences Naturelles* 197–210 (1952)
236. Gelineo, S., and Gelineo, A., *Compt. rend. soc. biol.*, **149**, 387–89 (1955)
237. Gelineo, S., and Gelineo, A., *Compt. rend. soc. biol.*, **149**, 565–68 (1955)

238. Gelineo, S., and Kolendic, M., *Bull. Acad. Serbe Sci.*, **12,** 39–43 (1953)
239. Gelineo, S., and Sokic, P., *Compt. rend. soc. biol.*, **147,** 138–40 (1953)
240. Gell, C. F., Polis, B. D., and Bailey, O., *Am. J. Physiol.*, **183,** 23–26 (1955)
241. Gellhorn, E., *Acta Neurovegetativa*, **11,** 90–93 (1955)
242. Gellhorn, E., and Feldman, J., *Am. J. Physiol.*, **133,** 670–75 (1941)
243. Genest, L. C., *Contribution à l'étude histologique du pancréas chez le rat blanc en hypothermie provoquée* (Berthod. Ed. Doctoral Thesis, Lyon Univ., Bourg, 60 pp., 1955)
244. Georges, G., and Cahn, J., *Anesthésie et analgésie*, **10,** 409–19 (1953)
245. Georges, G., and Cahn, J., *Compt. rend. soc. biol.*, **148,** 1806–10 (1954)
246. Georges, G., and Cahn, J., *Compt. rend. soc. biol.*, **149,** 1775–78 (1955)
247. Giaja, J., *Compt. rend. soc. biol*, **90,** 1087–89 (1924)
248. Giaja, J., *Compt. rend.*, **210,** 80–82 (1940)
249. Giaja, J., *Compt. rend.*, **225,** 436–37 (1947)
250. Giaja, J., *Compt. rend.*, **226,** 842–44 (1948)
251. Giaja, J., *Presse méd.*, **61,** 128–29 (1953)
252. Giaja, J., *Biologie méd.*, **42,** 545–80 (1953)
253. Giaja, J., *Bull. soc. chim. Biol.*, **36,** 445–53 (1954)
254. Giaja, J., *Bull. Acad. Natl. Méd.*, **138,** 519–21 (1954)
255. Giaja, J., *Rev. Pathol. gén et comparée*, **55,** 122–27 (1955)
256. Giaja, J., and Andjus, R., *Compt. rend.*, **230,** 1366–67 (1950)
257. Giaja, J., and Dimitrijevic, J. N., *Arch. intern. pharmacodynamie*, **45,** 342–60 (1933)
258. Giaja, J., and Markovic-Giaja, L., *Arch. Sci. physiol.*, **9,** C23–C34 (1955)
259. Giaja, J., and Markovic-Giaja, L., *Compt. rend. soc. biol.*, **149,** 2073–75 (1955)
260. Giaja, J., and Markovic-Giaja, L., *Compt. rend. soc. biol.*, **150,** 9–11 (1956)
261. Giaja, J., Markovic-Giaja, L., and Pavlovic, V., *Arch. intern. physiol.*, **63,** 413–21 (1955)
262. Giaja, J., Markovic-Giaja, L., and Sokic, P., *Compt. rend. soc. biol.*, **149,** 447–49 (1955)
263. Giaja, J., and Popovic, V., *Compt. rend.*, **234,** 1210–11 (1952)
264. Giaja, J., and Popovic, V., *Compt. rend.*, **234,** 2012–14 (1952)
265. Giaja, J., and Popovic, V., *Compt. rend.*, **235,** 89–90 (1952)
266. Giaja, J., and Popovic, V., *Compt. rend.*, **236,** 1700–1 (1953)
267. Giaja, J., and Popovic, V., *Compt. rend.*, **237,** 1360–2 (1953)
268. Ginglinger, A., and Kayser, C., *Ann. physiol. physicochim. biol.*, **5,** 710–61 (1929)
269. Giorgio, A. M. di, *Boll. soc. ital. biol. sper.*, **29,** 1989–90 (1953)
270. Giorgio, A. M. di, *Boll. soc. ital. biol. sper.*, **29,** 1990–1 (1953)
271. Giorgio, A. M. di, *Boll. soc. ital. biol. sper.*, **30,** 1401–2 (1954)
272. Giorgio, A. M. di, *Boll. soc. ital. biol. sper.*, **30,** 1402–3 (1954)
273. Gollan, F., *Am. J. Physiol.*, **171,** 727 (1952)
274. Gollan, F., *Federation Proc.*, **13,** 57 (1954)
275. Gollan, F., Blos, P., and Schuman, H., *Am. J. Physiol.*, **171,** 331–40 (1952)
276. Gollan, F., and Kory, R. C., *Abstracts XIXth International Physiological Congress* (Montréal, 398–99, 1953)
277. Gollan, F., Phillips, R., Jr., Grace, J. T., and Jones, R. M., *J. Thoracic Surg.*, **30,** 626–30 (1955)

278. Gollan, F., Tysinger, D. S., Jr., Grace, J. T., Kory, R. C., and Meneely, G. R., *Am J. Physiol.*, **181**, 297–303 (1955)
279. Goltz, F., *Pflügers Arch. ges. Physiol.*, **51**, 570–614 (1892)
280. Gosset, J., *Mém. Acad. Chir.*, **80**, 350–5 (1954)
281. Gouzon, B., Pruneyre, A., and Donnet, V., *Compt. rend. soc. biol.*, **148**, 2039–40 (1954)
282. Graham, G. R., and Joels, N., *J. Physiol. (London)*, **130**, 39P (1955)
283. Grant, R., *Am. J. Physiol.*, **160**, 285–90 (1950)
284. Grosse-Brockhoff, F., and Schoedel, W., *Arch. exptl. Pathol. Pharmakol.*, **201**, 417–42 (1943)
285. Guareschi, A., and Cazzullo, C. L., *Boll. soc. ital. biol. sper.*, **30**, 222–5 (1954)
286. Gwathmey, O., and Pierpont, H., *Am. Surgeon*, **21**, 827–34 (1955)
287. Gyermek, L., *Arch. exptl. Pathol. Pharmakol.*, **209**, 456–64 (1950)
288. Hajdukovic, S., Herve, A., and Vidovic, V., *Experientia*, **10**, 343–44 (1954)
289. Halpern, B. V., and Liakopoulus, P., *Compt. rend. soc. biol.*, **148**, 955–59 (1954)
290. Hamilton, J. B., Dresbach, M., and Hamilton, R. S., *Am. J. Physiol.*, **118**, 71–6 (1937)
291. Hansen, D. B., *J. Appl. Physiol.*, **6**, 645–49 (1954)
292. Harris, A. S., Bisteni, A., Russel, R., Brigham, J. C., and Firestone, J. E., *Science*, **119**, 200–3 (1954)
293. Harris, J. E., Gehrsitz, L. B., and Nordquist, L., *Am. J. Ophthal.*, **36**, 39–50 (1953)
294. Hart, J. S., *Can. J. Zool.*, **31**, 80–98 (1953)
295. Heagy, F. C., and Burton, A. C., *Am. J. Physiol.*, **152**, 407–16 (1948)
296. Hegnauer, A. H., and D'Amato, H. E., *Am. J. Physiol.*, **178**, 138–42 (1954)
297. Hegnauer, A. H. and Covino, B. G. (Personal communication 1956)
298. Hegnauer, A. H., and Penrod, K. E., *Observations on the pathologic physiology in the hypothermic dog.* (A. F. Technical Report Nr 5912, U. S. A. Air Force, Air Materiel Command, Wright-Patterson Air Force Base, Dayton, Ohio, 108 pp., 1950).
299. Hegnauer, A. H., Shriber, W. J., and Haterius, H. O., *Am. J. Physiol.*, **161**, 455–65 (1950)
300. Heim, F., and Haas, B., *Arch. exptl. Pathol. Pharmakol.*, **226**, 395–402 (1955)
301. Heintzen, P., *Pflügers Arch. ges. Physiol.*, **259**, 381–99 (1954)
302. Herlant, M., *Acad. roy. Belg., Bull. Classe Sci.*, [5] **40**, 408–15 (1954)
303. Heroux, O., and Hart, J. S., *Am. J. Physiol.*, **177**, 219–21 (1954)
304. Heymans, J. F., *Arch. inter. pharmacodynamie*, **25**, 1–225 (1919)
305. Hiebel, G., Bonvallet, M., and Dell, P., *Semaine hôp. Paris*, **30**, 2346–53 (1954)
306. Hirvonen, L., *Acta Physiol. Scand.*, **36**, 38–46 (1956)
307. Hirvonen, L., and Lybeck, H., *Acta Physiol. Scand.*, **36**, 29–37 (1956)
308. Hoff, H. E., and Geddes, L. A., *J. Appl. Physiol.*, **7**, 416–24 (1955)
309. Holtkamp, W., *Z. Kreislaufforsch.*, **34**, 579–87 (1942)
310. Homann, W., *Krebsarzt*, **9**, 223–30 (1954)
311. Hong, S. K., *Am. J. Physiol.*, **183**, 628 (1955)
312. Hook, W. E., and Stormont, R. T., *Am. J. Physiol.*, **133**, P334–P335 (1941)
313. Hopps, J. A., and Bigelow, W. G., *Surgery*, **36**, 833–49 (1954)
314. Horvath, A., *Pflügers Arch. ges. Physiol.*, **12**, 278–82 (1876)
315. Horvath, A., *Verhandl. der physik.-med. Gesellschaft, Würzburg*, **14**, 55–120 (1880)

316. Horvath, S. M., in *Cold Injury, Trans. Ist Conf.* (Ferrer, M. I., Ed. Josiah Macy Jr. Foundation, New York, N. Y., 248 pp., 1952)
317. Horvath, S. M., Hutt, B. K., Spurr, G. B., and Stevens, G. E., *Science*, **118**, 100–101 (1953)
318. Huggins, R., Breckenridge, C., and Hoff, H. E., *Am. J. Physiol.*, **163**, 153–58 (1950)
319. Huguenard, P., *Anesthésie et analgésie*, **11**, 583–97 (1954)
320. Huguenard, P., and Fayot, G., *Anesthésie et analgésie*, **12**, 557–91 (1955)
321. Huxley, J. S., Webb, C. S., and Best, A. T., *Nature*, **143**, 683–84 (1939)
322. Iampietro, P. F., Buskirk, E. R., and Fregly, M. J., *Am. J. Physiol.*, **183**, 629 (1955)
323. Irving, L., *Condor*, **57**, 362–5 (1955)
324. Irving, L., and Krog, J., *J. Appl. Physiol.*, **6**, 667–80 (1954)
325. Jaeger, E. C., *Condor*, **50**, 45–6 (1948)
326. Jaeger, E. C., *Condor*, **51**, 105–9 (1949)
327. Jaeger, E. C., *Natl. Geographic Mag.*, **103**, 273–80 (1953)
328. Jaulmes, C., Delga, J., and Richard, S., *Compt. rend. soc. biol.*, **147**, 1220–22 (1953)
329. Jaulmes, C., Delga, J., Benitte, A., and Richard, S., *Compt. rend. soc. biol.*, **149**, 1386–89 (1955)
330. Jensen, C., and Ederstom, H. E., *Am. J. Physiol.*, **183**, 340–44 (1955)
331. Jentzer, A., *Ann. Endocrinol.*, **13**, 705–23 (1952)
332. Jongbloed, J., *J. Physiol. (Paris)*, **45**, 477–89 (1953)
333. Juvenelle, A., Bergstrand, A., Lind, J., Norberg, B., Olsen, P., and Wegelius, C. W., *J. Physiol. (Paris)*, **45**, 633–54 (1953)
334. Juvenelle, A., Lind, J., and Wegelius, C., *Presse méd.*, **60**, 973–78 (1952)
335. Juvenelle, A., Lind, J., and Wegelius, C., *Am. Heart J.*, **47**, 692–736 (1954)
336. Kaminski, Z., *Sprawozdana Czynnosci Posiedzen Polskiej Akad. Umiejetnosci*, **52**, 499 (1951)
337. Kass, G. H., *Am. J. Med.*, **18**, 146–9 (1955)
338. Kayser, C., *Ann. Physiol. Physicochim. biol.*, **15**, 1087–1219 (1939)
339. Kayser, C., *Compt. rend. soc. biol.*, **131**, 525–27 (1939)
340. Kayser, C., *Compt. rend. soc. biol.*, **131**, 893–95 (1939)
341. Kayser, C., *Ann. Physiol. Physicochim. biol.*, **16**, 1–68 (1940)
342. Kayser, C., *Mammalia*, **14**, 105–25 (1950)
343. Kayser, C., *Arch. Sci. Physiol.*, **4**, 361–78 (1950)
344. Kayser, C., *Arch. Sci. Physiol.*, **6**, 193–212 (1952)
345. Kayser, C., *Arch. Sci. Physiol.*, **9**, C5–C21 (1955)
346. Kayser, C., *Acta Anesthésiol.*, **3**, 103–21 (1955)
347. Kayser, C., *Acta Neurovegetativa*, **11**, 38–59 (1955)
348. Kayser, C., *Rev. Pathol. gén. et comparée*, **55**, 704–28 (1955)
349. Kayser, C., *Compt. rend. soc. biol.*, **149**, 1655–57 (1955)
350. Kayser, C., and Hiebel, G., *Presse Méd.*, **60**, 1699–702 (1952)
351. Kayser, C., and Hiebel, G., *Compt. rend. soc. biol.*, **147**, 1626–29 (1953)
352. Kayser, C., and Hiebel, G., *Compt. rend.*, **236**, 526–28 (1953)
353. Kayser, C., Jacob, M., and Lucot, M. A., *Compt. rend. soc. biol.*, **148**, 1853–56 (1954)
354. Kayser, C., Rietsch, M. L., and Lucot, M. A., *Arch. Sci. Physiol.*, **8**, 155–94 (1954)

355. Kayser, C., Rohmer, F., and Hiebel, G., *Rev. neurol.*, **84,** 570–78 (1951)
356. Kerpel-Fronius, E., Mester, A., Szy, S., Barka, I., Zsamar, E., and Kelemen, I., *Acta Physiol. Acad. Sci. Hung.*, **7,** 103–11 (1955)
357. Khalil, H. H., and MacKeith, R. C., *Brit. Med. J.*, (4890), 734–36 (1954)
358. Kind, L. S., *Proc. Soc. Exptl. Biol. Med.*, **85,** 371–72 (1954)
359. Kisch, B., Simons, A., and Weyl, P., *Biochem. Z.*, **204,** 179–91 (1929)
360. Koch-Isenburg, L., *Umschau Wiss u. Tech.*, **55,** 335–38 (1955)
361. Koella, W. P., and Ballin, H. M., *Arch. intern. physiol.*, **62,** 369–80 (1954)
362. Koella, W. P., and Ballin, H. M., *Electroencephalog. Clin. Neurophysiol.*, **6,** 629–34 (1954)
363. Koella, W. P., Ballin, H. M., and Gellhorn, E., *Arch. intern. physiol.*, **62,** 54–69 (1954)
364. Koizumi, K., *Am. J. Physiol.*, **183,** 35–43 (1955)
365. Koizumi, K., Malcolm, J. L., and Brooks, C. M., *Am. J. Physiol.*, **179,** 507–12 (1954)
366. Koskimies, J., *Experientia*, **4,** 274–76 (1948)
367. Kostial, K., and Vouk, V. B., *J. Physiol. (London)*, **132,** 239–41 (1956)
368. Kramer, K., and Reichel, H., *Klin. Wochschr.*, **23,** 192–98 (1944)
369. Kramer, K., and Reichel, H., *Klin. Wochschr.*, **23,** 201–4, (1944)
370. Krieg, H., *Naturw. Rundschau*, **5,** 25–6 (1952)
371. Krijgsman, B. J., Kamer, J. C. van de, Lennep, E. W. van, and Stock, A., *Acta Physiol. et Pharmacol. Neerl.*, **1,** 63–81 (1950)
372. Krog, H., and Monson, M., *Am. J. Physiol.*, **178,** 515–16 (1954)
373. Krog, H., Monson, M., and Irving, L., *J. Appl. Physiol.*, **7,** 349–54 (1955)
374. Kroll, F. W., *Deut. med. Wochschr.*, **77,** 879–80 (1952)
375. Kruta, V., *J. Physiol.*, **47,** 667–70 (1955)
376. Kuhl, W. J., Jr., Beck, E. M., Gershberg, H., and Ralli, E. P., *Federation Proc.*, **13,** 534 (1954)
377. Kuhl, W. J., Jr., Beck, E. M., Gershberg, H., Street, E., and Ralli, E. P., *Metabolism*, **4,** 143–52 (1955)
378. Kunlin, J., Jaulmes, C., and Laborit, H., *Mém. acad. chir.*, **79,** 664–70 (1953)
379. Laborit, H., *Resistance et soumission en physiobiologie.* (Masson, Paris, France, 117 pp., 1954)
380. Laborit, H., *Anesthésie et analgésie*, **12,** 369–77 (1955)
381. Laborit, H., *Hibernation et risque opératoire.* (XVIe Congrès International de Chirurgie, Copenhague, Imprimerie Médicale et Scientifique, Bruxelles, Belgique, 59 pp., 1955)
382. Laborit, H., Favre, R., Guittard, R., and Laborit, G., *Presse Méd.*, **63,** 223–27 (1955)
383. Laborit, H., Favre, R., Guittard, R., Laborit, G., and Buchard, F., *Anesthésie et analgésie*, **12,** 593–608 (1955)
384. Laborit, H., and Huguenard, P., *Pratique de l'hibernothérapie en Chirurgie et Médecine.* (Masson, Paris, France, 256 pp., 1954)
385. Laborit, H., and Huguenard, P., *Compt. rend. soc. biol.*, **150,** 145–47 (1956)
386. Laborit, H., and Laborit, G., *Excitabilité neuro-musculaire et équilibre ionique. Intérêt pratique en chirurgie et en hibernothérapie.* (Masson, Paris, France, 107 pp., 1955)
387. La Franca, S., *Z. exptl. Pathol. Therap.*, **6,** 1–15 (1909)

388. Lainé P., Zacouto, F., Coraboeuf, E., Saumont, R., and Gaillard, R., *Compt. rend. soc. biol.*, **150**, 116–18 (1956)
389. Laufberger, V., *Z. ges. exptl. Med.*, **42**, 570–613 (1924)
390. Laufman, H., *J. Am. Med. Assoc.*, **147**, 1201–12 (1951)
391. Laur, C. M., *Rev. Pathol. gén. et comparée*, **55**, 1147–51 (1955)
392. Lavenda, N., Bartlett, R. G., Jr., and Kennedy, V. E., *Am. J. Physiol.*, **184**, 624–26 (1956)
393. Leeds, S. E., *J. Am. Med. Assoc.*, **152**, 1409–13 (1953)
394. Leeds, S. E., Gray, N. N., and Cook, O. S., *Surg. Gynecol. Obstet.*, **91**, 399–404 (1950)
395. Lemaitre, M., *Z. Biol.*, **106**, 415–25 (1954)
396. Lemaitre, M., *Z. Biol.*, **106**, 426–35 (1954)
397. Lewis, F. J., *Minnesota Med.*, **38**, 77–81 (1955)
398. Lian, C., Cahn. J., Courbier, R., Jean, E., and Dubrasquet, M., *Bulletin Acad. Natl. Méd.*, **139**, 374–77 (1955)
399. Libet, B., Fazekas, J. F., Meirowsky, A. M., Campbell, E. H., and Himwich, H. E., *Am. J. Physiol.*, **129**, 404P–405P (1940)
400. Lidicker, W. Z., Jr., and Davis, W. H., *Proc. Soc. Exptl. Biol. Med.*, **89**, 640–42 (1955)
401. Loeb, R. F., *J. Am. Med. Assoc.*, **104**, 2177–82 (1935)
402. Longo, V. G., Berger, G. P. v., and Bovet, D., *J. Pharmacol. Exptl. Therap.*, **111**, 349–59 (1954)
403. Lorenz, K., *Der Vogelzug*, **3**, 4–10 (1932)
404. Lougheed, W. H., Sweet, W. H., White, J. C., and Brewster, W. R., *J. Neurosurg.*, **12**, 240–55 (1955)
405. Lubinska, L., *Acta biol. exptl.* (Lodz), **16**, 65–71 (1952)
406. Lundberg, A., *Acta Physiol. Scand.*, **15**, Suppl. 50, 67 pp. (1948)
407. Lundberg, A., and Laget, P., *Arch. Sci. Physiol.*, **3**, 193–204 (1949)
408. Lutz, W., *Klin. Wochschr.*, 727–33 (1943II)
409. Lutz, W., *Z. Kreislaufforsch.*, **36**, 625–39 (1944)
410. Lyman, C. P., *J. Exptl. Zool.*, **109**, 55-78 (1948)
411. Lyman, C. P., *Am. J. Physiol.*, **166**, 638–43 (1951)
412. Lyman, C. P., and Chatfield, P. O., *Am. J. Physiol.*, **163**, 731 (1950)
413. Lyman, C. P., and Chatfield, P. O., *Physiol. Rev.*, **35**, 403–525 (1955)
414. Lyman, C. P., and Fawcett, D. W., *Cancer Research*, **14**, 25–8 (1954)
415. Lyman, C. P., and Hastings, B., *Am. J. Physiol.*, **167**, 633–37 (1954)
416. Lyman, C. P., and Leduc, E. M., *J. Cellular Comp. Physiol.*, **41**, 471–91 (1953)
417. Madden, R. F., Stemler, F. W., and Hiestland, W. A., *Am. J. Physiol.*, **180**, 121–23 (1955)
418. Magliocca, R., *Ormonologia*, **12**, 346–54 (1953)
419. Maier, A., Forster, E., and Kayser, C., *Compt. rend. soc. biol.*, **149**, 398–400 (1955)
420. Maier, A., Forster, E., Schaff, G., and Kayser, C., *Compt. rend. soc. biol.*, **149**, 568–70 (1955)
421. Maier, A., Forster, E., Schaff, G., and Kayser, C., *Compt. rend. soc. biol.*, **149**, 1485–87 (1955)
422. Malméjac, J., Boiteau, H., and Neverre, H., *Compt. rend. soc. biol.*, **149**, 1549–52 (1955)

423. Malméjac, J., Chardon, G., and Neverre, G., *Compt. rend. soc. biol.*, **148,** 1243–46 (1954)
424. Malméjac, J., Neverre, G., and Malméjac, C., *J. Physiol. (Paris)*, **48,** 624–27 (1956)
425. Malméjac, J., Neverre, G., Montero, M., and Fredenucci, R., *J. Physiol. (Paris)*, **48,** 628–32 (1955)
426. Malméjac, J., and Plane, P., *Compt. rend. soc. biol.*, **149,** 677–79 (1955)
427. Malméjac, J., Plane, P., and Malméjac, C., *J. Physiol. (Paris)*, **48,** 632–34 (1956)
428. Malorny, G., *Arch. exptl. Pathol. Pharmakol.*, **222,** 80–1 (1954)
429. Mantecchini, P., and Jorio, L., *Ormonologia*, **14,** 154–64 (1954)
430. Marceron, L., *Rev. Pathol. gén. et comparée*, **55,** 1103–7 (1955)
431. Markovic-Giaja, L., *Compt. rend. soc. biol.*, **150,** 558–61 (1956)
432. Markovic, L., and Giaja, G., *J. Physiol. (Paris)*, **43,** 69–73 (1951)
433. Martin, G., et Du Caillar, J., *Minerva chir.*, **10,** 300–4 (1955)
434. Massopust, L. C., Jr., *Univ. Colo. Studies*, **54,** 28–9 (1954)
435. Masuda, H., Ohara, M., and Katsura, S., *Tohoku J. exptl. Med.*, **58,** 49–55 (1953)
436. Matson, J. R., *J. of Mammol.*, **27,** 203–212 (1946)
437. Mayer, J., and Barrnett, R. J., *Yale J. Biol. and Med.*, **26,** 38–45 (1953)
438. McBirnie, J. F., Pearson, F. G., Trusler, G. A., Karachi, H. H., and Bigelow, W. S., *Can. J. of Med. Sci.*, **31,** 421–30 (1953)
439. Meda, E., *Med. sper.*, **23,** 3–15 (1953)
440. Meriel, Bolinelli, Calazel, Cassagneau, Galinier, Bichain, and Lafaille, *Rev. Pathol. gén. et comparée*, **55,** 921–6 (1955).
441. Mettinen, M., *Ann. Med. Internae Fenniae*, **43,** 298–304, (1954)
442. Metz, B., and Andlauer, P., *J. Physiol. (Paris)*, **44,** 293–97 (1952)
443. Metz, B., and Mours-Laroche, M. F., *Compt. rend. soc. biol.*, **149,** 579–582 (1955)
444. Meyer, D. K., Westfall, B. A., and Platner, W. S., *Am. J. Physiol.*, **184,** 553–56 (1956)
445. Miles, B. E., and Churchill-Davidson, H. C., *Anesthesiology*, **16,** 230–34 (1955)
446. Miller, J. A., Jr., and Miller, F. S., *Surgery*, **36,** 916–31 (1954)
447. Miller, J. A., Jr., and Miller, F. S., *Am. J. Physiol.*, **183,** 645 (1955)
448. Minett, F. C., *J. Comparative Pathol. and Therap.*, **65,** 197–219 (1955)
449. Montini, T., and Paoletti, G., *Arch. fisiol.*, **55,** 218–29 (1955)
450. Morel, F., and Combrisson, A., *Rapport au Commissariat à l'Energie Atomique* (420), 5 pp. (1955)
451. Morin, G., Donnet, V., Coignet, J., and Salamon, G., *Les bases physiologiques des méthodes thérapeutiques d'hibernation et de déconnection* (XVe Congrès des Pédiatres de Langue Française, Sopic, Marseille, France, 90 pp., 1955)
452. Morrison, P. R., Ryser, F. A., and Strecker, R. L., *J. Mammal.*, **35,** 376–86 (1954)
453. Müller, E., *Acta Neurovegetativa*, **11,** 146–58 (1955)
454. Nahas, G. G., Dubost, C., and Schiessle, W., *Presse Méd.*, **63,** 491–92 (1955)
455. Nahas, G. G., Schiessle, W., and Aimé, L., *J. Physiol. (Paris)*, **47,** 709–14 (1955)
456. Nahas, G. G., and Wapler, C., *Presse Méd.*, **62,** 1668–70 (1954)
457. Nardone, R. M., *Am. J. Physiol.*, **182,** 364–68 (1955)

458. Nardone, R. M., Wilber, G., and Muacchia, X. J., *Am. J. Physiol.*, **181,** 352–56 (1955)
459. Nashat, F. S., and Neil, E., *J. Physiol.* (*London*), **127,** 59P–60P (1955)
460. Niazi, S. A., and Lewis, F. J., *Surgery*, **36,** 25–32 (1954)
461. Niazi, S. A., and Lewis, F. J., *Surg. Forum, Cong. Am. Coll. Surgeons*, **5,** 113–15 (1954–55)
462. Nicholls, D., and Rossiter, R. J., *Endocrinology*, **56,** 547–59 (1955)
463. Nielsen, K. C., *Acta Med. Scand.*, **148,** 409–10 (1954)
464. Nitschke, A., *Z. ges. exptl. Med.*, **82,** 227–35 (1932)
465. Nitschke, A., and Maier, E., *Z. ges. experimentl. Med.*, **82,** 212–16 (1932)
466. Noel, R., Cosnier, J., and Genest, L. C., *Bulletin Assoc. Anatomistes*, (85), 388–92 (1955)
467. Olivereau, M., *Compt. rend. soc. biol.*, **149,** 536–39 (1955)
468. Omachi, A., Ginski, J. M., and Eto, M., *Am. J. Physiol.*, **179,** 660 (1954)
469. Osborn, J. J., *Am. J. Physiol.*, **175,** 389–98 (1953)
470. Page, L. B., *Am. J. Physiol.*, **181,** 171–78 (1955)
471. Pagliari, M., *Ormonologia*, **12,** 425–30 (1953)
472. Parkes, A. S., "Preservation of living cells at low temperatures," 250–68, *Lectures on the scientific basis of medicine*, Vol. II (The Athlon Press, London, England, 380 pp., 1954)
473. Parkes, A. S., and Smith, A. U., *J. Physiol.* (*London*), **124,** 61P–62P (1954)
474. Parkins, W. H., Berr, M., and Vars, H. M., *Surgery*, **38,** 38–47 (1955)
475. Pavlovic, V., *Compt. rend. soc. biol.*, **149,** 2216–17 (1955)
476. Pembrey, M. S., *J. Physiol.* (*London*), **18,** 363–79 (1895)
477. Perkins, W. J., *Elec. Eng.*, **27,** 394–96 (1955)
478. Peruzzo, L., and Forni, R. B., *Presse Méd.*, **61,** 1463 (1953)
479. Peters, K., *Arch. exptl. Pathol. Pharmakol.*, **226,** 570–76 (1955)
480. Peters, K., and Lehr, H., *Arch. exptl. Pathol. Pharmakol.*, **221,** 365–72 (1954)
481. Pichotka, J., Creutzfeldt, O., and Höfler, W., *Arch. exptl. Pathol. Pharmakol.*, **225,** 314–22 (1955)
482. Pichotka, J., Creutzfeldt, O., and Höfler, W., *Arch. exptl. Pathol. Pharmakol.*, **225,** 323–34 (1955)
483. Pichotka, J., Creutzfeldt, O., and Höfler, W., *Arch. exptl. Pathol. Pharmakol.*, **225,** 335–41 (1955)
484. Pichotka, J., Kugelen, B. von, and Damann, R., *Arch. exptl. Pathol. Pharmakol.*, **220,** 398–413 (1952)
485. Pierpont, H. C., and Blades, B., *Am. Surgeon*, **21,** 739–44 (1955)
486. Platner, W. S., and Hosko, M. D., Jr., *Am. J. Physiol.*, **174,** 273–76 (1953)
487. Pontius, R. G., Brockman, H. L., Hardy, E. G., Cooley, D. A., and Debakey, M. E., *Surgery*, **36,** 33–8 (1954)
488. Popovic, V., *Bull. Acad. Serbe Sci.*, **4,** 121–36 (1951)
489. Popovic, V., *Bull. Acad. Serbe Sci.*, **4,** 215–23 (1951)
490. Popovic, V., "Contribution à l'étude de la thermogenèse de l'homéotherme refroidi," Monograph, *Acad. Serbe Sci.*, **199** (7), 156 pp. (1952)
491. Popovic, V., *Arhiv. biol. nauka*, **5,** 161–70 (1953)
492. Popovic, V., *Compt. rend. soc. biol.*, **148,** 845–46 (1954)
493. Popovic, V., *Arch. Sci. Physiol.*, **9,** C219–C229 (1955)
494. Precht, H., *Z. Naturforsch.*, **4b,** 26–35 (1949)

495. Precht, H., Christophersen, J., and Hensel, H., *Temperatur und Leben* (Springer-Verlag, Berlin-Göttingen-Heidelberg, Germany, 514, pp. 1955)
496. Prior, C., and Vegni, L., *Gazz. Intern. Med. Chir.*, **59,** 1185–93 (1954)
497. Prior, C., and Vegni, L., *Presse Méd.*, **63,** 824 (1955)
498. Prior, C., Vegni, L., and Bacchini, I., *Gazz. Intern. Med. Chir.*, **59,** 1244–52 (1954)
499. Punt, A., *Acta Physiol. Pharmacol. Neerl.*, **4,** 439–40 (1955)
500. Quinn, M., Bass, D. E., and Kleeman, C. R., *Proc. Soc. Exptl. Biol. Med.*, **83,** 660–61 (1953)
501. Rabbione, B., *Ormonologia*, **14,** 145–53 (1954)
502. Raffucci, F., Lewis, F. J., and Wangensteen, O. H., *Proc. Soc. Exptl. Biol. Med.*, **83,** 639–40 (1953)
503. Ransmeier, R. E., and Gerard, R. W., *Am. J. Physiol.*, **179,** 663–64 (1954)
504. Ranson, S. W., and Magoun, H. W., *Ergeb. Physiol.*, **41,** 56–163 (1939)
505. Reinberg, A., and Stolkowski, J., *Ann. Endocrinol.*, **13,** 599–609 (1952)
506. Renzo, M., *Ormonologia*, **15,** 106–16 (1955)
507. Richards, A. G., Simonson, E., and Visscher, M. B., *Am. J. Physiol.*, **174,** 293–98 (1953)
508. Riedesel, M. L., and Folk, G. E., *Am. J. Physiol.*, **179,** 665 (1954)
509. Ripstein, C. B., Friedgood, C. E., and Solomon, N., *Surgery*, **35,** 98–103 (1954)
510. Robertson, W. van B., and Peyser, P., *Am. J. Physiol.*, **166,** 277–83 (1951)
511. Rodbard, S., Saiki, H., and Malim, A., *Federation Proc.*, **9,** 107 (1950)
512. Rodbard, S., Saiki, H., Malim, A., and Young, C., *Am. J. Physiol.*, **167,** 485–97 (1951)
513. Rodbard, S., and Tolpin, M., *Am. J. Physiol.*, **151,** 509–15 (1947)
514. Romijn, C., and Lokhorst, W., *Poultry Sci.*, **34,** 649–54 (1955)
515. Rosomoff, H. L., and Gilbert, R., *Am. J. Physiol.*, **183,** 19–22 (1955)
516. Rosomoff, H. L., and Holaday, D. A., *Am. J. Physiol.*, **179,** 85–88 (1954)
517. Ross, D. N., *Guy's Hosp. Repts.*, **103,** 97–115, 116–138 (1954)
518. Rudler, J. C., *Presse Med.*, **63,** 1883 (1955)
519. Ruhe, C. H., and Horn, R. H., *Am. J. Physiol.*, **182,** 325–30 (1955)
520. Ryser, F. A., and Morrison, P. R., *Auk*, **71,** 253–66 (1954)
521. Saathoff, J., and Opitz, E., *Pflügers Arch. ges. Physiol.*, **255,** 492–98 (1952)
522. Sabiston, D. C., Jr., Theilen, E. O., and Gregg, D. E., *Am. J. Physiol.*, **179,** 668 (1954)
523. Sabiston, D. C., Jr., Theilen, E. O., and Gregg, D. E., *Surgery*, **38,** 498–505 (1955)
524. Sarajas, H. S., *Acta Physiol. Scand.*, **32,** 28–38 (1954)
525. Scott, J. L., Jr., and Engel, F. L., *Endocrinol.*, **53,** 410–22 (1953)
526. Scott, J. W., McQueen, D. A., and Callaghan, J. C., *Electroencephalog. Clin. Neurophysiol.*, **5,** 465 (1953)
527. Schaeffer, G., and Thibault, O., *Compt. rend. soc. biol.*, **139,** 855–56 (1945)
528. Schaumann, W., *Arch. exptl. Pathol. Pharmakol.*, **224,** 48–54 (1955)
529. Scherf, D., Blumenfeld, S., Golbey, M., Ladopoulus, C., and Roth, F., *Am. Heart J.*, **49,** 218–36 (1955)
530. Schmid, F., *Compt. rend. soc. biol.*, **149,** 1470–72 (1955)
531. Schmidt-Nielsen, B., and Forster, R. P., *J. Cellular Comp. Physiol.*, **44,** 233–46 (1954)

532. Schoedel, W., *Acta Neurovegetativa*, **11**, 60–71 (1955)
533. Sealander, J. A., Jr., *Am. Midland Naturalist*, **46**, 257–311 (1951)
534. Sealander, J. A., Jr., *Ecology*, **33**, 63–71 (1952)
535. Sealander, J. A., Jr., *J. Mammal.*, **33**, 206–18 (1952)
536. Sealander, J. A., Jr., *Biol. Bull.*, **104**, 87–99 (1953)
537. Sealander, J. A., Jr., and Walker, B. Q., *Proc. Arkansas Acad. Sci.*, **8**, 153–62 (1955)
538. Sealander, J. A., Jr., and Young, H., *Proc. Arkansas Acad. Sci.*, **7**, 21–31 (1955)
539. Sellers, E. A., Reichman, S., and Thomas, N., *Am. J. Physiol.*, **167**, 644–50 (1951)
540. Sellers, E. A., Reichman, S., Thomas, N., and You, S. S., *Am. J. Physiol.*, **167**, 651–55 (1951)
541. Senèque, J., Chatelin, C. L., and Huguenard, P., *Rev. Pathol. gén. et comparée*, **55**, 766–819 (1955)
542. Senger, I. F., *Arkhiv Patol., S.S.S.R.*, Nr 3, 41-4 (1955)
543. Severinghaus, J. W., and Stupfel, M., *J. Applied Physiology*, **8**, 81–7 (1955)
544. Shanes, A. M., *Am. J. Physiol.*, **177**, 377–82 (1954)
545. Siems, M. V., Horvath, St. M., Spurr, G. B., Hutt, B. K., and January, L. E., *Am. J. Physiol.*, **181**, 325–29 (1955)
546. Silvette, H., and Britton, S. W., *Am. J. Physiol.*, **100**, 685–92 (1932)
547. Simpson, S., *J. Physiol. (London)*, **28**, XXXVII–XL (1902)
548. Simpson, S., and Herring, P. T., *J. Physiol. (London)*, **32**, 305–11 (1955)
549. Sinelnikoff, E. J., *Pflügers Arch. ges. Physiol.*, **221**, 549–61 (1929)
550. Sjöstrand, T., *Physiol. Revs.*, **33**, 202–28 (1953)
551. Skrer, N., *Compt. rend. soc. biol.*, **149**, 71–4 (1955)
552. Smith, D. J., *Am. J. Physiol.*, **171**, 528–37 (1952)
553. Smith, A. U., Lovelock, J. E., and Parkes, A. S., *Nature*, **173**, 1136–37 (1954)
554. Smith, L. W., and Fay, T., *Am. J. Clin. Pathol.*, **10**, 1–11 (1940)
555. Spach, C., Lucot, M. A., and Kayser, C., *Compt. rend. soc. biol.*, **149**, 2250–54 (1955)
556. Spoelstra, A. J. G., and Hoitink, A. W. J. H., *Acta Physiol. Pharmacol. Neerl.*, **4**, 437–38 (1955)
557. Spurr, G. B., Hutt, B. K., and Horvath, S. M., *Am. J. Physiol.*, **178**, 275–82 (1954)
558. Spurr, G. B., Hutt, B. K., and Horvath, St. M., *Am. J. Physiol.*, **179**, 139–45 (1954)
559. Stapel, S., *Arch. intern. physiol.*, **61**, 330–37 (1953)
560. Steadman, L. T., Ariel, I., and Warren, S. L., *Cancer Research*, **3**, 471–74 (1943)
561. Stefanovic, M. P., *Monograph, Acad. Serbe Sci.*, **198**, 84 (summary in French) (1952)
562. Stefanovic, M. P., *Bull. soc. chim. Biol.*, **36**, 1151–61 (1954)
563. Stevens, C. E., Angelo, S. A.d', Paschkis, K. E., Cantarow, A., and Sunderman, F. W., *Endocrinology*, **56**, 143–56 (1955)
564. Stone, C. P., and Mason, W. A., *J. Comp. Physiol. Psychol.*, **48**, 456–62 (1955)
565. Storer, J. B., and Hempelmann, L. H., *Am. J. Physiol.*, **171**, 341–48 (1952)
566. Stullken, D. W., and Hiestand, W. A., *Proc. Soc. Exptl. Biol. Med.*, **86**, 253–55 (1954)
567. Sunderman, F. W., and Haymaker, W., *Am. J. Med. Sci.*, **213**, 562–71 (1947)
568. Suomalainen, P., *Ann. Acad. Sci. Fennicae*, [A] **53**, (7), 68 pp. (1939)

569. Suomalainen, P., *Sitzber. finn. Akad. Wiss.*, 131–44 (1953)
570. Suomalainen, P., and Granström, T., *Exptl. Cell Research*, Suppl. 3, 335–38 (1955)
571. Suomalainen, P., and Suvanto, I., *Ann. Acad. Sci. Fennicae* [A], 3–20 (1953)
572. Svihla, A., Bowman, H., and Ritenour, R., *Am. J. Physiol.*, **172,** 681–83 (1953)
573. Svorad, D., *Ceskoslov. Fysiol.*, **4,** 145–51 (1955)
574. Svorad, D., *Ceskoslov. Fysiol.*, **4,** 152–62 (1955)
575. Swan, H., and Zeavin, I., *Ann. Surg.*, **139,** 385–96 (1954)
576. Swan, H., Zeavin, I., Blount, S. G. Jr., and Virtue, R. W., *J. Am. Med. Assoc.*, **153,** 1081–85 (1953)
577. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V., *Ann. Surg.*, **138,** 360–75 (1953)
578. Swim, H. E., and Parker, R. F., *Proc. Soc. Exptl. Biol. Med.*, **89,** 549–53 (1955)
579. Szekeres, C., Faller, J., and Torok, T., *Acta Physiol. Acad. Sci. Hung.*, **6,** Suppl., 99–100 (1954)
580. Talbott, J. H., In *Cold Injury, Trans. 1st Conf.*, pp. 145–80, Ferrer, M. I., Ed., Josiah Macy Jr. Foundation, New York, N. Y., 248 pp., 1952)
581. Tanche, M., *Compt. rend. soc. biol.*, **149,** 1561–64 (1955)
582. Tanche, M., and Klepping, J., *Compt. rend. soc. biol.*, **149,** 1564–67 (1955)
583. Ten Cate, J., Horsten, G. P., and Koopman, L. J., *Electroencephalog. Clin. Neurophysiol.*, **1,** 231–34 (1949)
584. Terzian, H., *Rev. Neurol.*, **91,** 445–53 (1954)
585. Terzian, H., and Ruberti, R., *Riv. Neurol.*, **24,** 686–702 (1954)
586. Thibault, O., *Compt. rend. soc. biol.*, **140,** 940–42 (1946)
587. Tourpaev, T. M., *Doklady Akad. Nauk S.S.S.R.*, **102,** 323–26 (1955)
588. Trautwein, W., and Dudel, J., *Pflügers Arch. ges. Physiol.*, **260,** 104–15 (1954)
589. Trautwein, W., Gottstein, U., and Federschmidt, K., *Pflügers Arch. ges. Physiol.*, **258,** 243–60 (1953)
590. Tum Suden, C., *Am. J. Physiol.*, **149,** 589–96 (1947)
591. Turner, M., Berard, E., Turner, N., and Franco, N., *Electroencephalog. Clin. Neurophysiol.*, **8,** 25–39 (1956)
592. Turner, R. S., and Turner, M. M., *Endocrinology*, **36,** 32–40 (1945)
593. Tysinger, D. S., Jr., Grace, J. T., and Gollan, F., *Am. Heart J.*, **50,** 816–22 (1955)
594. Valerio, I., and Carli, F. de, *Arch. fisiol.*, **53,** 247–75 (1953)
595. Veghelyi, P., and Harsing, L., *Klin. Wochschr.*, **33,** 908–9 (1955)
596. Vegni, L., and Prior, C., *Boll. soc. ital. biol. sper.*, **30,** 780–82 (1954)
597. Vegni, L., and Prior, C., *Gazz. Intern. Med. Chir.*, **49,** 1067–94 (1954)
598. Vegni, L., and Prior, C., *Experientia*, **11,** 455–56 (1955)
599. Verhandlungen der Deutschen Pharmakologischen Gesellschaft, 20. Tagung, *Arch. Exptl. Pathol. Pharmakol.*, **222,** 1–256 (1953)
600. Vernejoul, R. de, *Anesthésie et analgésie*, **12,** 773–820 (1955)
601. Vernejoul, R. de, and Courbier, R., *Marseille Chir.* (5), 451–65 (1954)
602. Vernejoul, R. de, Metras, H., Jean, E., Courbier, R., and Richelme, H., *Presse Méd.*, **63,** 1531–33 (1955)
603. Vernejoul, R. de, Metras, H., Ottavioli, P., Jean, E., and Courbier, R., *Presse Méd.*, **62,** 1679–80 (1954)
604. Vernejoul, R. de, Metras, H., Ottavioli, P., Jean, E., and Courbier, R., *Minerva Chir.*, **10,** 346–55 (1955)

605. Verzár, F., and Vidovic, V. L., *Helv. Physiol. et Pharmacol. Acta*, **9**, C13–C14 (1951)
606. Verzár, F., Vidovic, V., and Hajdukovic, S., *J. Endocrinol.*, **10**, 46–53 (1953)
607. Vidovic, V., *Experientia*, **8**, 304–6 (1952)
608. Vidovic, V., and Popovic, V., *J. Endocrinol.*, **11**, 125–33 (1954)
609. Villalobos, T. J., Adelson, E., Barila, T. G., and Fraction, G. F., *Proc. Soc. Exptl. Biol. Med.*, **89**, 192–96 (1955)
610. Vlasin, Z., and Filkuka, J., *Arch. exptl. Pathol. Pharmakol.*, **227**, 414–26 (1956)
611. Walther, A., *Du Bois Reymond Arch. Physiol.*, 25–51 (1865)
612. Ware, A. G., Hill, R. M., and Schultz, F. H., *Am. J. Physiol.*, **149**, 657–66 (1947)
613. Wendt, C. F., *Z. physiol. Chem.*, **249**, IV (1937)
614. Wener, J., Hoff, H. E., Scott, H., and Winter, M., *Am. J. Physiol.*, **161**, 289–93 (1950)
615. Werz, R. von, *Arch. exptl. Pathol. Pharmakol.*, **222**, 78–9 (1954)
616. Wiedemann, H. R., and Haupt, H., *Z. Kinderheilk.*, **73**, 355–68 (1953)
617. Willems, *Arch. exptl. Pathol. Pharmakol.*, **222**, 85–6 (1954)
618. Winterstein, H., *Arch. exptl. Pathol. Pharmakol.*, **223**, 1–18 (1954)
619. Woodbury, L. A., Hecht, H. H., and Christophersen, A. R., *Am. J. Physiol.*, **164**, 307–18 (1951)
620. Wyss, O. A. M., *Pflügers Arch. ges. Physiol.*, **229**, 599–635 (1932)

TISSUE METABOLISM (PHARMACOLOGICAL ASPECTS)[1,2]

By Maynard B. Chenoweth and George L. Ellman
Biochemical Research Department, The Dow Chemical Company, Midland, Michigan

INTRODUCTION

It is axiomatic that drugs act upon cells and many pharmacologists have sought to systematize the amorphous *logos* of pharmacology through researches in the chemistry of the drug-cell interactions. This review will seek what progress has been made in recent years in this direction. We have asked, "What has this study contributed to the understanding of the intracellular events which cause the characteristic pharmacologic action of the drug under study?" There is an enormous production of literature dealing with this area of research. Close inspection reveals that much of the work may be most delicately described as irrelevant to this question.

To establish a basis for considering an investigation to have been truly helpful certain propositions are offered below. Not very many studies meet all these qualifications, and very many studies scarcely meet any of them. It is probable that as little attention will be paid to these directions for planning research as appears to have been paid to the similar advice offered a decade ago by Welch & Bueding (1). Nevertheless; (*a*) The experiments must be performed on the appropriate cells of organs primarily affected by the drug, preferably while the primary function of this system is under constant monitoring. (*b*) The experimental species employed must be carefully chosen after the gross pharmacology of the drug is known in several species. (*c*) Concentrations of drug added to tissue systems *in vitro* should be less than 10 times that calculated from an even distribution of the usual pharmacologic dose throughout the body in the species chosen. They should be less than 5 times greater than any accurately known analytical data for the organ and species involved. (*d*) Metabolic changes found *in vitro* must be confirmed *in vivo*. If this can not be done, the reasons why it can not must be defended. (*e*) Inhibitors added in addition to the drug under study must be used in minimal concentrations needed to accomplish a well-established action. (*f*) Results in any system must be specific to the chemical or pharma-

[1] Examination of the literature ended June 30, 1956. Papers prior to 1950 were not generally consulted. Following Annual Reviews of Physiology practice, abstracts are not usually quoted.

[2] The following abbreviations are used in this chapter: ATP (adenosinetriphosphate); ADP (adenosinediphosphate); DNP (dinitrophenol); INH (isonicotinoyl hydrazide); PABA (*p*-aminobenzoic acid); RNA (ribonucleic acid); TPN (triphosphopyridine nucleotide); R. Q. (respiratory quotient); PIA (positive inotropic action); FAc (fluoroacetic acid); PAH (*p*-amino hippurate); FCit (fluorocitric acid); Cit (citrate); CoA (coenzyme A).

cological analogs of the original drug and must not be produced by inactive members of the series. Exceptions must be explained. Non-specific compounds should be inert at reasonable concentrations.

EFFECTS ON TISSUE METABOLISM

Muscle

Heart.—A fascinating pharmacological problem involving heart muscle is the mechanism by which the cardiac glycosides produce an increased force of contraction. This effect is induced only in heart muscle preparations which are fatigued, and the extent of the increase in contractile force is limited to the "normal" amplitude. This is in contradistinction to the effect of sympathomimetic amines which can produce an increase in contractile force greatly in excess of the "normal" upon unfatigued, as well as fatigued myocardium. This effect of cardiac glycosides is spoken of as a "positive inotropic action" (PIA) a term which ought not to be applied to skeletal muscle (inos = heart). Further, except for the curious case of semi-anoxic skeletal muscle (2, 3) a similar effect is not produced elsewhere. The PIA need not be related to the conduction and impulse formation action of the glycosides, and, indeed, it most probably is not. Experiments must be designed carefully to avoid confusion of end results because of this. Theories offering explanations of the PIA must take cognizance of the speed with which the genins act; full effects being obtainable in a few minutes (4). There is isotopic carbon evidence that digitalis action persists beyond its presence [Fischer, Sjoerdsma & Johnson (5)], [Kuschinsky, *et al.* (6)]. The latter workers have adduced evidence for the formation of a glycoside-lipide combination in heart muscle which is subsequently released, perhaps accounting for the fact that the action of digitalis persists even though there is none left in the heart. Muscle contracts, wherein lies its interest. Studies of muscle pharmacology in which there is no assessment of the contractile behavior need little comment.

The impressive review by Wollenberger in 1949 brought together the information to that time and analyzed most critically the meaning of the work (7). Recently, Bing has reviewed myocardial metabolism, particularly from the point of view of his work in man (8), while Olson has reviewed molecular events in cardiac failure (9). [See also (10 to 13).] Among the recent researches, a study by Greiner (14) of the relationship of the force of contraction of papillary muscles to their high energy phosphate content is outstanding. It appears to the reviewers that the specific muscle preparations in which changes in high energy phosphate were observed were too seriously damaged or depressed to enable one to conclude that high energy phosphate depletion was related to the failure under more moderate conditions, or that the glycosides act in this area.

The fact that dinitrophenol prevents the PIA of cardiac glycosides seems well established (15, 16, 17). It does not influence the PIA of epineph-

rine, which is interpreted to suggest separate metabolic pathways from the glycosides [Gruhzit & Farah (16)]. However, skeletal muscle depressed by dinitrophenol is stimulated by k-strophanthin [Köhler, *et al.* (18)].

Based upon experiments with the frog heart and a variety of inhibitors, Ellis concluded that the PIA of the cardiac glycosides [and probably other compounds having similar actions (19)] is "not dependent upon the functional integrity of the oxidative metabolism, the Krebs-tricarboxylic acid cycle, or the Embden-Meyerhof metabolic chain as long as an adequate metabolism for producing energy remains. This places the site of action of the agents in the area of metabolism involved in utilization of chemical energy for muscular work" (20).

Lee showed that isometric contractions of papillary muscle may be recorded photographically while the muscle is in a respirometer flask (21, 22) and he found that the increased oxygen consumption induced by ouabain occurs well after the maximum increase in PIA and more nearly parallels the contracture at the end of the experiment. [Such contracture is associated with decreased sulfhydryl content (23).] This differs from the effect of epinephrine which increases the force of contraction immediately and increases the oxygen consumption immediately [Lee (24)].

Some comments on choice of preparation seem indicated. In our experience the dog heart-lung preparation does not give positive inotropic responses indiscriminately and it may be regarded as the final arbiter. In a study of this preparation, Price & Helrich (25) found that a pH decrease of only 0.4 distinctly depressed the heart-lung preparation and such a variation in pH was noted in their control preparations. They used only preparations within 0.04 pH units of that of their control for their studies of the effects of anesthetics. The isolated cat papillary muscle offers much in the way of simplicity as a method for the study of isolated ventricular muscle and a considerable background of information is now available. Although these muscles contain parallel muscle fibers and are thus damaged at only one region, the interior cells are not oxygenated and one works with a functionally "hollow" fusiform mass of heart cells, coated with endocardium. Variability in the quantitative response to drugs has been traced to excessive variation in the application of tension to the muscle and when this is controlled, remarkably uniform results may be obtained [Bennett (26)]. The Langendorf isolated perfused heart, particularly of the cat, can be extremely stable and permits a determination of nongaseous metabolites rather readily [Chenoweth & Koelle (27)]. The objection that the Langendorf preparation is not doing work must be taken into consideration in the design of experiments. The isolated auricle has the advantage that it contracts spontaneously, it is thin enough for oxygen to diffuse into it readily and several pieces may be obtained from single animals. It has been explored extensively with regard to enzymatic inhibitors (28 to 32). The influences of various metabolic inhibitors upon contractility, rate, and action potential are particularly well-defined by Gardner & Farah (29). The perfused amphibian

heart has the advantages of durability, economy, and simplicity. Further, it is resistant to anoxia and Ellis has made good use of this fact in his analysis of glycosidal action (20). Effects obtained upon it, however, can not always be duplicated in mammalian heart preparations.

The use of heart muscle slices to study metabolic effects of the cardiac glycosides is convenient, but Fischer, Huber & Langemann indicated that a slice becomes equivalent to an homogenate in one hour and these workers could not consistently duplicate earlier findings (33). Oxygen consumption is usually increased by cardiac glycosides (34 to 38). More uniform results seem to be obtained when the respiration of the slice is somewhat depressed [Langemann, Brody & Bain (58)]. A rough correlation of *in vivo* potency with *in vitro* activity was obtained, but exceptions were noted [Herrmann, Flamboe & Chen (35)]. Little or no effect upon enzymatic systems was reported by Reiter & Barron (39). Many studies report marked qualitative differences between the glycosides. As such differences are difficultly detected *in vivo*, it seems likely that the *in vitro* results are artifacts.

The relative ease with which contractile proteins may be isolated from muscle has promoted numerous studies of drug effects upon these systems, most of which are included in the comprehensive review of Hasselbach & Weber (40). [See (41, 42) for other pertinent reviews.] Little work has been done with inactive glycosides and a chilling effect upon speculation concerning mechanisms should be produced by Wollenberger's (43) experiments which showed that cardio-inactive *allo*-emicymarin and hexahydroscillaren A were just as effective as emicymarin and scillaren A in stimulating the polymerization of actin from heart muscle.

The phosphocreatine content of mammalian cardiac muscle was carefully assayed by Fawaz & Hawa (44) using exceptional care to prevent *post-mortem* changes. They found phosphocreatine concentrations in normal heart three times those reported by previous workers and found that barbiturate-failed hearts contain increased phosphocreatine, from which they concluded that the mechanism of heart failure could scarcely be attributed to a lack of production of high energy phosphate. Similarly, phosphorylating ability of mitochondria isolated from dog heart during failure induced in the heart-lung preparation was not different from controls, according to Brody, Palmer & Bennett (45). On the other hand, dog heart-lung preparations that were failed with sodium fluoroacetate showed very severe phosphocreatine depletion, but little change in ATP content [Fawaz (46)]. It may be remarked that the glycosides will not reverse failure induced by fluoroacetate (26), so the two sets of observations could be regarded as quite different in meaning.

Digitoxin slows the phosphorus uptake into all fractions of guinea pig heart, decreasing the myocardial content of organic phosphorus according to Harvey (47) who also noted that pentobarbital had qualitatively the same actions as digitoxin and confirmed the finding that phosphocreatine content was elevated by barbiturates.

Lorber (48) has made use of an elegant modification of the completely isolated mammalian heart to study energy metabolism in failure, finding that failure is primarily a deterioration of mechanical efficiency. A backlog of information has accumulated on the use of rat ventricular strip (49, 50, 51). Studies of the effect of cardiac glycosides on the human heart have been made by Bing and his co-workers under varying clinical conditions of cardiac failure and normalcy. Only minimal changes in the extractable metabolites of the coronary blood were found (52) and little effect was observed on the sodium and potassium balances (53). This latter observation suggests that inactive glycosides should be examined, for it seems quite likely that a variety of materials might exert effects on sodium-potassium-calcium balances (54). Interrelations of steroids, hormones, cardiac glycosides and potassium were observed years ago which still require further study (55).

Sodium permeability appears related to electrical potentials in heart muscle, according to findings of Weidmann (56) and differences in electrical behavior of heart and skeletal muscle may perhaps explain their differing responses to drugs. Quite low concentrations of cardiac glycosides inhibit the active phase of cation transport in human erythrocytes, but the significance of this is somewhat obscured by the activity of cardio-inactive lactones (in much higher concentrations) and the inactivity of other substances having a positive inotropic action [Kahn & Acheson (57)].

Reiter (58) has found strophanthin to increase intracellular sodium concentrations in rat ventricle strips. The increase is related to the magnitude of the stimulant effect.

Tanz, Clark & Whitehead have found 9-alpha fluoro hydrocortisone to produce a PIA and to cause significant increases in muscle Na content (59). Leaf has found sodium to accumulate in isolated tissues generally when their metabolism was depressed (60).

Miscellaneous observations include the following: Although 10^{-4}M quinidine depresses respiration of heart muscle (61), concentrations which have little effect on oxygen consumption markedly reduce the contraction height of papillary muscles (62). The influence of metabolic inhibitors upon the "staircase" phenomena has been examined (63). Lüllmann has reviewed the action of the xanthines on the heart, including metabolic aspects (64). An extensive review by Giotti includes a great deal of information on the biochemical basis of the action of many agents on the heart (65).

Skeletal muscle.—Because colchicine produced hind limb weakness, it was examined on isolated frog sartorius preparations and while considerable effect was reported, the concentrations required to produce significant changes were out of range of those active *in vivo* [Ferguson (66)]. It appears well-defined that k-strophanthin retards potassium outflow during the activity of frog sartorius muscle in concentrations not more than 10 to 100 times those active on cardiac muscle [Schatzmann & Witt (67)]. (See above under *Heart.*) The isolated rat diaphragm will contract anaerobically at 27°C. in 0.38 per cent glucose and such contractions are still responsive to

epinephrine (68). The effects of a series of sympathomimetic amines on glycogenolysis in this preparation reveal that isoproterenol is the most active (69). Pentobarbital has been found to inhibit the effect of insulin on glucose utilization and glycogen content of noncontracting rat diaphragm (70).

Local anesthetics increased the transverse impedance of toad gastrocnemius muscle *in situ* but related compounds without local anesthetic activity had no such action, nor did a number of compounds capable of altering muscle metabolism [Crepax (71)]. Frog rectus muscle in drug-induced contracture showed no change in the levels of ATP and ADP. A decrease in creatine phosphate and some evidence of the splitting of two other unidentified phosphorous esters was noted [Fleckenstein, *et al.* (72)]. The effect of monobromoacetic acid on the metabolism of frog muscle was studied by Hermans (73), who found that loss of excitability coincides with the hydrolysis of ATP and during contracture there is but feeble metabolic activity.

Central Nervous System

Central nervous system function, unlike heart or liver, is not expressed as multiples of the function of a single cell-type but by highly ramified interworkings of groups of cells. Critical cell bodies are actually sparsely distributed throughout the brain substance, which in the bulk is comprised of supportive cells, vascular materials, and fibrous tracts subserving neuronal cell bodies. While brain tissue readily forms slices, homogenates, minces, and mitochondrial suspensions, it seems unsophisticated in the extreme to anticipate that much of value can be learned from the countless *in vitro* experiments in which such preparations have been subjected to overwhelming concentrations of illogically chosen pharmacological agents. The volume of such observations could only be handled by electronic card sorting machinery and probably constitutes the mass of experimental evidence in support of "Toman's Law."[3]

The reviewers have attempted to select certain studies which employed the best methods available and approached the study of this exquisite mechanism with some grasp of its complexity. The exceptionally critical review of theories of general anesthesia by Butler (74) is required reading. His conclusions about mechanisms prepare one for the finding of Levy & Featherstone (75) that xenon and nitrous oxide have no effect upon *in vitro* oxidation of glucose or pyruvate nor upon oxidative phosphorylation. Indeed, anesthesia with xenon, especially, seems to defy metabolic explanations. Hunter & Lowry (76) have very recently reviewed the effect of barbiturates on oxidation and phosphorylation and the action of electrical impulses applied to mitochondrial suspensions, but as long as convulsant

[3] A remark by Dr. J. E. P. Toman at a meeting a few years ago to the effect that "enough of anything will inhibit anything" was quickly caught up and is referred to facetiously in this country as "Toman's Law."

barbiturates seem indistinguishable from anesthetic ones, it may all be misleading [Brody & Bain (77)]. Divergences of opinion on the actions of anesthetics are expressed by Quastel (78), Rosenberg (79) & Grenell (80) whose papers should be studied by those with serious interest in this field.

The dramatic end point of a generalized convulsive seizure as a result of the administration of pharmacological agents or the equally dramatic induction of general anesthesia seems to have provoked a feeling that these two differing end points should be provoked by intracellular mechanisms just as different. Observations of this, that, or the other function, chemical or physiological, of brains so affected are often made without consideration of the fact that these changes are more than likely a result, not the cause of the effect. With so much difficulty attendant upon interpretation of gross responses, the more delicate nuances of drug actions in the cases of chlorpromazine or reserpine can not yet be ferreted from the conflicting data already obtained (81 to 87). The actions of ethanol on man's most unique properties will not be elucidated from rat brain slices *in vitro*, according to Sutherland, Hine & Burbridge (88) who found differences between rat and human cortex metabolism during *in vitro* exposure to ethanol and expressed dissatisfaction with such approaches.

In order to examine the relative effects of fluoroacetate and fluorobutyrate as convulsant poisons in the dog, Hendershot & Chenoweth (89) made use of the isolated cortical slab technique originated by Kristiansen & Courtois (90). Electrical activity of the cerebral cortex of curarized dogs was recorded while the drugs were injected into the isolated section in very small doses. Upon the instant that the electroencephalograph recorded convulsive activity in the isolated section, it was removed and analyzed for citrate. Suitable antagonists, monoacetin (versus fluoroacetate) and monobutyrin (versus fluorobutyrate) were injected systemically and prevented the characteristic convulsive seizures of the isolated slab, but not citrate accumulation. It was evident that citrate accumulation per se was not the cause of the excessive electrical activity. This study is of interest generally because of the approach, rather than the specific problem involved. It would seem that the technique has application whenever it is desired to correlate biochemical and physiological changes in a certain part of the cerebral cortex. A somewhat similar approach in which the general behavior of the animal was the criterion for sampling was used by Shideman & Seevers (91) in experiments in which the brains of monkeys were widely exposed under local anesthesia and the effects of stimulants and depressants elicited. When the full effect of the drug was observed in the animal, the exposed brain was deluged instantly with liquid air, broken out and analyzed. Using such a technique, no significant effect on ATP, phosphocreatine or inorganic phosphate was observed when chloral hydrate, pentylenetetrazole, or 5-ethyl-5(1,3-dimethylbutyl)-barbituric acid were administered. A decrease in phosphocreatine was only observed when d-tubocurarine was given. This suggests that many of the changes described in brain constituents under the

influence of stimulants or depressants are related to the general anoxic, hyperventilated or hyperactive state of the animal. Very marked changes in the glycogen content of mouse brain under the influence of different convulsants were reported by Chance (92). The increment in glycogen content in various areas of the brain correlated, in general, with the expectation for that area from classical pharmacology. As the correlation and changes were so definite, the observations warrant extension in other species and further investigation generally. Studies of the distribution in the central nervous system of two C^{14}-labelled analgesics turned out to be discouragingly noninformative, for both were distributed similarly, yet one was pharmacologically active and the other was not [Brierley & McCoubrey (93)]. A pair of chemically similar diols, one convulsant and one depressant, were found to have dissimilar modes of action upon pig heart succinoxidase systems [Neufeld, Greenberg & Slater (94)]. The fluorescent acridone studied by Mayer & Bain (95) is exceptionally interesting because of the sensitivity of the fluorescent method of analysis. It was found to concentrate markedly in the cerebral cortex after intravenous injection and concentrations of 17 μg./gm. induced convulsions. It was found distributed throughout the cortex in proportion to the content of cell bodies. To examine the analeptic action of amiphenazole (2,4-diamino-5-phenyl-thiazole), Shulman (96) treated rats on a thiamine-free diet with this compound plus a pyrimidine moiety of thiamine (2-methyl-4-amino-5-bromomethyl pyrimidine) and after a period of adaptation lasting from 7 to 10 days, the rats showed no signs of vitamin B_1 deficiency for a period of up to 9 weeks. Control animals on the same diet without the drugs all died with vitamin B_1 deficiency symptoms in 5 weeks. Amiphenazole may enter into pathways involving thiamine, but it is not certain that this is related to the analeptic action. One may note that nikethamide (N-diethyl nicotinamide) quite unrelatedly, will replace nicotinic acid in deficient diets, or produce a rapid, marked increase in liver size and protein [Dessauer & Brazda (97)]. Similar relations between the convulsant action of 2-methyl-4-amino-5-hydroxymethyl pyrimidine and pyridoxine have been demonstrated by Shintani (98), but in this case the relationship appears to be much more closely connected with the convulsant activity, for it is well-known that pyridoxine deficiency can produce convulsions. The work of Pfeiffer, *et al.*, on the relation of pyridoxine to convulsions caused by hydrazides, is summarized and extended in a recent paper (99). Certain ultraviolet spectra of proteins isolated from the brain and liver of cocaine or aldrin treated mice revealed patterns tentatively regarded as characteristic for the drug and organ [Annau (100)].

Brain ATP in morphine tolerant rats was found to be unchanged according to Abood, Kun & Geiling (101). A slight increase in brain cytochrome-*c* oxidase activity during chronic morphinization was followed by a marked depression during withdrawal [Wang & Bain (102)]. But although morphine and its phenolic relatives catalyze the transfer of electrons from reduced DPN to ferricytochrome-*c* in the absence of enzyme and the potency as

transfer agents correlates with their potency as cytochrome-*c* reductase-DPN inhibitors, all of these phenomena could be observed only with concentrations of 10^{-3}M and Wang & Bain (103) were "disappointed."

A direct relation between the anticonvulsant action of acetazoleamide and its ability to inhibit carbonic anhydrase in brain tissue was established by Millichap, Woodbury & Goodman (104). Sulfanilamide was shown to be a less potent inhibitor *in vitro* and less potent *in vivo* than acetazoleamide. Brain concentrations of both inhibitors of carbonic anhydrase closely correlated when compared on an equally anticonvulsant basis with the concentrations required for inhibition of the enzyme *in vitro*.

The anticonvulsant effect of diphenyl hydantoin is associated with an increase in the active outflow of sodium from cerebral cells, according to results with radioactive sodium. The electroshock threshold correlated with the ratio of extracellular to intracellular sodium [Woodbury (105)].

Recent reviews include the following: Mechanism of action and metabolism of anticonvulsants were reviewed by Toman & Taylor (106). Some of the literature on the cellular actions of barbiturates and closely related work is reviewed by Richards & Taylor (107). The effects of toxic substances on central nervous system chemistry are discussed in (108, 109, 110).

Liver

Liver has been employed as a source of enzymes, mitochondria, partially reconstituted metabolic systems, etc. to which nearly every known pharmacologically active agent has been added, usually without the slightest interest in the fact that it was liver per se under study. It is not useful to review these papers under the "Liver" rubric.

Few pharmacological agents exert a distinct effect upon the liver and of these, carbon tetrachloride has received the greatest attention. Richter has found that the Q_{O_2}, succinoxidase and cholineoxidase activity are higher in carbon tetrachloride treated livers than in normal livers. He also found a decrease in its ability to methylate nicotinamide and guanidoacetic acid (111). Using doses of carbon tetrachloride which did not produce extensive liver damage, Hove & Hardin (112) found that in rats on a diet deficient in vitamin E, creatine synthesis from guanidoacetic acid and methionine declined very markedly. The same changes were observed to a lesser degree in vitamin E deficient rats and its was suggested that carbon tetrachloride precipitates an acute vitamin E deficiency. The activity of xanthine oxidase is said to be increased during carbon tetrachloride poisoning, both *in vivo* and *in vitro* (113, 114). Large cytoplasmic particles which are rich in succinicdehydrogenase are depleted in activity but the maximum activity per unit nitrogen is not changed, suggesting that the particles are lost altogether. The particles containing uricase show an interesting increase in activity per unit nitrogen when recovery processes set in [Thomson & Moss (115)]. Increase in the liver glutathione content in carbon tetrachloride poisoned rats on a diet deficient in sulfur-containing amino acids has been shown to be the

result of regeneration of liver, not necrosis [Eden & Harrison (116)]. Bruns & Neuhaus (117) have observed in carbon tetrachloride poisoned mice, the activity of serum aldolase and phosphohexoisomerase increase 15 to 20-fold while that in liver drops 34–53 per cent. These experiments are taken to show that during toxic injury to liver cells, glycolytic enzymes may enter the blood. Thus, in a general sense in organ systems altered by disease or drug action, it is not permissible to equate measured reduced enzyme activities with reduced enzyme synthesis for the enzyme may diffuse away from partially damaged cells.

Brauer (118) reviewed the liver as an organ, paying particular attention to the effect of drugs upon it. His own work with slices and perfusions of rat liver indicates that bromsulphonphthalein (BSP) uptake is not inhibited by cyanide, fluoride, or mercuric ions and that the selective removal of BSP from blood plasma by liver is apparently an adsorptive, not a metabolic phenomenon (119). Perfusion of the isolated liver is a useful technique recently improved by Young, Prudden & Stirman (120). It has been applied by Miller & Axelrod (121) to the study of the metabolism of cortisone. Cirrhotic livers lose the capacity to reduce the α-β unsaturated ketone at the C3 position, which activity is prominent in normal liver. They turned to the isolated perfused dog liver for the study of the normal metabolism of hydrocortisone (122). Perfusion of bullfrog livers by Goldner & Jauregui (123) indicated that alloxan inhibits glycogenolysis weakening the evidence for the pancreatic origin of alloxan hypoglycemia. That alloxan has a prominent effect upon liver metabolism is indicated by the observations of Bass, *et al.* (124) who found that alloxan increased the desoxyribose nucleic acid in the liver cell nucleus whereas pancreatectomy did not. The porphyria induced by Sedormid (allyl-isopropyl-acetyl carbamide) has been traced, using radiocarbon-tagged glycine, to the ability of this compound to block formation of catalase in liver. No changes in iron enzyme activity elsewhere were noted except for a decline in liver cytochrome-*c* which was probably due to the animal's weight loss [Schmid, Figen & Schwartz (125)].

Kidney

The observation of Handley & Lavik (126) that mercurial diuretics produce a depression of succinic dehydrogenase activity in kidney tissue which can be reversed by dimercaprol does not seem difficult to accept, for this enzyme is sulfhydryl-activated and should be inhibited by mercury. This depression was specific to kidney tissue both *in vivo* and *in vitro*. Histochemical studies on the site of action of mercurial diuretics by Farah, Cafruny & DiStefano (127) in which they stained kidney slices for protein-bound sulfhydryls revealed a markedly reduced sulfhydryl content after a mercurial diuretic was administered to rats. No changes were noted elsewhere and a graded dose response was obtained. Dimercaprol prevented or restored the sulfhydryl content, although cysteine did not. Similar observations were made by Ruskin & Ruskin (128) using a rat heart homogenate preparation.

However, Fawaz & Fawaz (129) concluded that blockade of the Krebs' cycle is not the primary cause of diuresis. DeGroot, *et al.* distinguished between mercurials and xanthines in their effects upon phosphate metabolism of rat kidneys (130).

Transport of para-amino hippurate (PAH), glucose, etc. appears to be blocked by fluoroacetate [Farah, Graham & Koda (131, 132)], [Taggart (133)]. Transport of PAH is inhibited by malonate and antimycin and as both compounds inhibit succinate oxidation, Dominguez & Shideman (134, 135) have concluded that this may be a cause and effect relationship. Schwalb, Bauernfeind & Hensel (136) found that doses of 20 to 65 mg./kg. of sodium fluoride in the dog produce a marked decrease in the clearance of PAH and creatine. This suggests that when any one of the major metabolic energy sources is interfered with, the action of a second drug may not be obtained.

Microorganisms

The polymyxins are reviewed by Newton (137) and some interesting pictures indicate they act upon the cell wall to cause disintegration of the organism. Radioactively tagged penicillin has not led to great understanding of the mode of action of penicillin, according to Cooper (138). General reviews of the mechanisms of antibacterial action have been presented by Umbreit (139, 140) and by Binkley (141). A review of the chemotherapy of viruses by Matthews & Smith (142) contains considerable discussion of the mechanisms of action of compounds exerting some deleterious effect on viruses. Older reviews in this area may be consulted by the interested reader (143, 144, 145). The effects of the major antibiotics on cell metabolism were covered in the review by Hunter & Lowry (76).

The antitubercular action of isonicotinoyl hydrazide (INH) is not covered extensively in other reviews. The compound definitely forms metal chelates [see Chenoweth (146) for a discussion of this phase of its action]. It has been suggested by Gangadharam & Sirsi (147) that its activity is due to reaction with iron, for it inhibits cytochrome oxidase, succinic oxidase and catalase. Knox, Albert & Rees (148) have shown that it is converted catalytically to diisonicotinoylhydrazine and isonicotinic acid by hemin. Such a mechanism of action is not incompatible with the observed finding that INH competes with pyridoxyl phosphate for the apoenzyme [Lichstein (149)]. Inhibition of rat liver cysteine sulfinic acid decarboxylase, a pyridoxine dependent enzyme, is reported by Davison (150) who found that pyridoxal phosphate isonicotinic acid hydrazone was formed. The reaction is slow and not readily reversible. Pyridoxine will prevent peripheral neuritis caused by INH [Zbinden & Studer (151)]. INH appears to be a generally active inhibitor, antagonizing mono-amine oxidase (152, 153) and the oxidation of Dopa (154).

Studies of the antituberculosis activity of aromatic bases containing the diphenyl nucleus, revealed that optimum activity occurred in those in which

the pK_a was not less than 8.0 and whose lipoid-water distribution coefficient was not less than 0.2. The most active compound also formed metal complexes which "may account for its high activity" [Cymerman-Craig, Rubbo & Pierson (155)]. The effect of biphenyl groups as inhibitors of respiration was examined in a series of compounds by Abood & Gerard (156), and upon the nucleic acid breakdown in growth of mycobacteria by Bernheim & DeTurk (157). Cymerman-Craig, *et al.* (158) observed similar requirements in a second series of heterocyclic bases and added that they must have a flat molecular area. The commercially important bisphenolic compounds were examined on the metabolism of animal tissue wherein hexachlorophene was found to inhibit succinic oxidase, cytochrome oxidase, and lactic dehydrogenase in concentrations around 10^{-5}M [Gould, Frigerio & Lebowitz (159)]. Similar results were obtained upon bacterial systems earlier [Gould, *et al.* (160)].

Dividing Cells

A cogent analysis of the problem of drug action on cell division from the point of view of the cytologist should be read by all who work in this area [Mazia (161)]. The effects of substituted phenols (162), purines (163, 164, 165), and urethane (166) have been reviewed *in extenso*. Attempts to analyze the mechanism of action of *N*-methyl formamide (167), podophyllin (168), and assorted metabolic inhibitors (169) have not produced general conclusions. Fluoride and iodoacetate were examined in the Walker tumor and in normal tissues and their effects suggest that phosphorylation differs only quantitatively (170). The unique arrest of spermatogenesis by nitrofurans was shown to parallel a decrease of the seminiferous tubules' ability to oxidize pyruvate *in vitro*. The effect can be duplicated by hypophysectomy and X-irradiation and it was concluded that the failure to utilize pyruvate was secondary to the lack of more mature cell forms in the tubules and not the cause of such lack [Featherstone, *et al.* (171)].

Carcinogenesis by chemicals has been the subject of a valuable book (172) and important reviews (173 to 177).

Endocrine System

A general review of possible mechanisms of action of hormones was presented by Hechter (178) in 1955, precluding need for review of earlier papers (but see 179), while Levine and Goldstein reviewed the mechanism of action of insulin in the same year (180) and Stadie the previous year (181). The mechanism of action of growth hormone was examined in review by Young (182). The action of adrenaline on metabolism was reviewed in 1953 by Sarzana, Rubino & Cascio (183). Thyroid function, thyroxine and antithyroid compounds attracted much attention in reviews (184 to 189). Hormonal (auxin) action in plants was reviewed recently by Olson (190). Many of the *in vitro* effects of thyroxine may be exerted through its ability to chelate metal ions (191, 192), for example, three moles of thyroxine bind one

mole of magnesium, although triiodothyronine is in an unionized phenolic form at physiological pH (pK_a 9.2) (191). Thyroxine uncouples phosphorylation from oxidation in mitochondria and this is antagonized by magnesium (193 to 196).

Anti-thyroid compounds have been divided into groups according to their inhibition of peroxidase or their reactivity with iodine [Fraser, Hanno & Pitney (197)]. They inhibit biochemical chlorination of tetracycline, probably by chelating the copper necessary for the reaction [Sekizawa (198)]. An interesting explanation for the goitrogenic action of PABA was offered by Hung & Delost (199) who showed that it depletes the available acetate of the thyroid by forming inactive acetyl PABA.

Neither cortisone nor insulin was found to have any effect on the metabolism of the perfused cow's udder (200) and little effect on glucose or pyruvate consumption of isolated guinea pig heart (201). Hydrocortisone is metabolized by kidney tissue *in vitro* to 11-β-hydroxy-Δ^4-androstene-3-17-dione which is a potent androgen, according to Ganis, *et al.* (202). Growth hormone increases asparagine-glutamine transaminase in young rats, but generally decreases nitrogen transfer enzyme activity in adults (203). A diethylamino derivative of testosterone inhibits rat liver succinoxidase non-competitively, possibly due to its diethylamino group (204). Estradiol stimulates a DPN-linked isocitric dehydrogenase (205) *in vitro*. Changes in 1-carbon fragment metabolism in surviving uteri from estradiol-treated rats are interpreted to favor reductive synthetic pathways supplying precursors for new growth [Mueller & Herranen (206)].

EFFECT OF DRUGS ON SPECIFIC ENZYME SYSTEMS

General Remarks

Receptor sites.—It is clear that the effect of a drug must eventually be explained on a molecular basis. The problem of the drug receptor site has only been intensively studied in a very few cases. An exceptional case is acetyl cholinesterase (207). Many of its inhibitors are alkylating agents which form covalent bonds with the receptor. The more difficult problem of the non-permanent type of binding characteristic of by far the majority of drugs in clinical use, has not as yet been solved for the general case.

Physiologically important enzymes.—There has been much confusion in the literature concerning the significance of enzymes which have been found to perform some sort of activity on a drug which the tissue system has never encountered. It should be clear from recent work in the field of enzymology that catalysis of many reactions requires only proper placement of a basic and an acidic group on a protein (208). The formation of an "ascorbic oxidase" is a case in point (209). The oxidation of aromatic rings may likewise be a nonphysiological process (210, 211, 212). In fact, boiling a tissue extract may activate enzymes by destroying an inhibitor (213). As a consequence, it is to be expected that a search throughout the animal and

plant kingdoms for a protein which can perform a selected activity will usually be rewarding. This, of course, does not mean that the substrate, which may be completely artificial, has any significance to the organism; nor does the fact of isolating and purifying, perhaps even to the state of crystallizing, a given enzyme, imply that the activity which is being examined has any physiological significance. It is probable that many enzymes are considerably larger and contain many more functional groups than required for their activity.

The multiplicity of enzymes.—Discussions of true and pseudo cholinesterase must now be tempered by the realization that this dichotomy is inadequate. Bergmann & Segal have pointed out that while psuedo cholinesterases in serum and tissue from dogs appear to be identical, true cholinesterase differs in various tissues (214). Paulescu, Vargiu & Gibertoni have reported a third cholinesterase in chick brain (215). Mitidieri (216) demonstrated clearly that xanthine dehydrogenase activity is associated with at least two electrophoretically separable proteins in serum. Kinetic evidence has been used by Bensusan, Derow & Walker to show that proteolytic activity of extracts of *Proteus vulgaris* must be due to at least two enzymes (217).

Significance of enzyme inhibitors.—More consideration ought to be given to the question of specificity of inhibitions than has been done in the recent literature. This problem is not simple and requires more than cursory work. It is certainly minimal to expect that inhibition by a drug should be classified as competitive, noncompetitive, or uncompetitive (218 to 221). To avoid ambiguity rates should be specified in terms of moles of substrate disappearing or product appearing; concentrations of materials should be given in standard, acceptable units; and in a general way, the entire reaction scheme needs to be tied into the bulk of scientific knowledge.

Specific Compounds

Alkylating agents.—Thymus and spleen adenosine triphosphatase as well as 5-nucleosidase activities have been shown to increase in animals treated with nitrogen mustard [DuBois, Peterson & Zins (222)]. By using fluoroacetate to block citric acid oxidation, it has also been shown that the rate of citric acid synthesis is decreased in the spleen and thymus, but it accumulated in the livers of mustard treated male dogs. As would be expected with an alkylating agent, the effect of even very low doses persists for a long time. No conclusions are drawn concerning the relation of these changes of enzymatic activities (223) to the toxic manifestations of mustard gas. Aerobic glycolysis of thymus lymphocytes, that is, lactic acid formation, is stimulated *in vitro* by low concentrations (10^{-5} and 10^{-4}M) but a slight inhibition begins at 10^{-3}M (224). Dose-response curves are *de rigeur* to settle this question.

Cyanide need not react with metals to be effective against enzymes. For example, Gawron, Keil & Glaid have shown that cyanide will react with

ribonuclease to split a disulfide bond, resulting in a loss of enzymatic activity. Although ribonuclease is not a sulfhydryl requiring enzyme, the disulfide bond is essential for maintaining the proper configuration at the enzymatic site and it is not involved in the activity of the enzyme (225). A similar circumstance was shown by Wood & Cooley in that cyanide reacted with cysteine *in vivo* to form a thiocyanate which subsequently cyclylized and was excreted (226).

Kamijo & Koelle showed that low doses of diisopropyl fluorophosphate would produce complete inactivation of pseudo cholinesterase but only partial inactivation of true cholinesterase. However, higher doses inactivated true cholinesterase more completely and only at these higher doses was potentiation of the nerve stimulus achieved (227). Similarly, Admiral, Myers & van Houten showed that there was a close correlation between the degree of inhibition of true cholinesterase by various compounds and their effects on intestinal motility in cats (228). On the other hand, Murtha, *et al.*, working with tetraethyl pyrophosphate, showed that cholinesterase did not have to be completely inactivated for complete blockade of nerve transmission. They concluded that cholinesterase was not primarily essential for nerve conduction although it must play a very large role (229). Strickland & Thompson have reported that potassium loss from brain slices is only produced by greater concentrations of cholinesterase inhibitors than are necessary to inhibit cholinesterase. Presumably the potassium loss is not directly connected with the inhibition of the cholinesterase (230). However, Hokin & Hokin have reported that acetylcholine increases the turnover rate of phospholipide in brain tissue. This effect is completely abolished by atropine. They suggest that acetylcholine makes the phospholipide more susceptible to the enzyme responsible for its turnover. This splitting of phospholipides releases potassium ion bound to phospholipide (231).

Wheeler, Morrow & Skipper have presented evidence for reaction products of the mustard gases with purines and pyrimidines. They have not suggested any structures however (232, 233).

Organo-metallic compounds.—While it is generally believed that mercurial compounds attack only sulfhydryl groups it should be noted that Gemmill & Bowman observed that invertase was inhibited by certain of these compounds (234). However, Sizer (235) has indicated that there are no free sulfhydryl groups in invertase. It is clear that further experimentation is needed to decide the meaning of these observations. While the mercurial diuretics cause large increases in the secretion of urine, Davenport, Chavré & Davenport report that the mercurials cause an inhibition of gastric secretions (236). Frieden and Naile have reported that phenylmercuric chloride partially inhibits ascorbic acid oxidase. This inhibition is reversible by thyroxin. They have shown that thyroxin is very effective in the chelation of copper, and suggest that thyroxin may be able to complex and remove the phenyl mercurial radical from the inhibited enzyme group of the ascorbic acid oxidase. Thus, thyroxin mimics a sulfhydryl compound in regenerating sulfhydryl

groups (237). It is of interest to note that Yall & Green have reported that *Micrococcus pyogenes aureus* forms at least two different ureases distinguishable by their inhibition by nitrofurazone, arsenicals, and mercurials. The normal cells form a urease resistant to these materials when grown in the absence of urea. The adaptive enzyme formed in the presence of urea is inhibited by these materials. However, in cells which are resistant to nitrofurazone, only the urease which is resistant to these materials is formed (238).

Certain titanium compounds have been shown to interfere with tyrosinase activity, presumably by complexing the substrate (239).

Displacing agents.—In work which has received considerable attention, Kewitz & Wilson were able to show that 2-pyridine aldoxime methiodide would reactivate cholinesterase which had been inactivated by various lethal alkylating agents. This material was designed for this specific purpose and represents a clear example of the application of chemical principles to a biological problem (240). Roy & Kuperman had shown very similar effects with this material against tetraethyl pyrophosphate intoxication (241). This represents the clearest case of a displacing agent as a pharmacologically important material.

Dinitrophenol (DNP) is perhaps best classified as a displacing agent. Present indications are that it operates by displacing a phosphate which is formed during electron transport from reduced diphosphopyridine nucleotide to oxygen. This unknown compound normally transfers its phosphate to ADP forming ATP; however, in the presence of DNP it appears that this material is decomposed to form inorganic phosphate, thus depriving the system of ATP formation. Only a very few specific suggestions have been made as to what this initial high energy phosphate compound might be. A most interesting one is that of Kaplan in which a 2-pyridone phosphate is attacked by DNP to release the pyridone, thereby stimulating the cycle of oxidative processes (242). The possibility of the formation of DNP phosphate has been mentioned but this material has never been shown to exist in mitochondrial preparations treated with DNP. The release of adenosinetriphophatase activity by DNP has been shown to be antagonized by phenylmercuric acetate and azide in mitochondria (243, 244). Phenylmercuric acetate is usually assumed to react with sulfhydryl groups. However, the fact that both azide and phenylmercuric acetate have the same effect is somewhat confusing, inasmuch as there is no evidence that azide is a sulfhydryl reagent. That stimulation of adenosinetriphosphatase activity by DNP is indeed a complicated process is attested by the results of Chappell & Perry who studied the complex magnesium and calcium interactions (245). Slater & Lewis have presented evidence for a DNP resistant phosphorylation at the level of the oxidation of α-ketoglutarate. This is in contradistinction to most DNP inhibited phosphorylations which are considered to be involved in the electron transfer system (246). On the other hand, Cohn had reported earlier that DNP does inhibit the entry of O^{18} into succinic acid formed by oxidation of α-ketoglutarate in the presence of O^{18} phosphate (247).

Grisolia reports that digitoxin and quinidine increase the effect of DNP on uncoupling of oxidative phosphorylation (248). A variety of effects have been reported which add to the list of evidences that DNP interferes with ATP formation. Aisenberg & Potter report that DNP depresses the activation of acetate, presumably due to depletion of ATP production (249). Similarly, DNP affects production of penicillin very markedly without affecting respiration of *Penicillium chrysogenum* (250). Born & Bülbring report the effects of DNP on guinea pig *Taenia coli* (251). Schacter reports that DNP not only accelerates the breakdown of high energy phosphate, but also of ester phosphate; making not only ADP available to accept new phosphate but other ester phosphates may be formed, too (252). It should be noted in passing that uncoupling of phosphorylation is apparently characteristic of many compounds which could possibly form some sort of enolic or phenolic phosphate ester; e.g., salicylates, barbiturates, peptides, tetracyclines, halophenols, thyroxin [Brody (253)].

Attempts to explain the effects of salicylates have been numerous. The fact that sodium salicylate inhibits sulfate exchange in chondroitin sulfuric acid in slices of cartilage may enhance our understanding of this phenomenon (254), for the actions of salicylates on pathologic joint conditions are noteworthy. Brody suggests that the salicylate-induced changes in metabolic rates, the glycogenolytic effect, hyperglycemia, and increased heat production after brain stem transection may well be explained by their ability to uncouple phosphorylation (253).

Marks has shown that barbiturates inhibit the acetylation of sulfanilamide by pigeon liver preparations. However, since all barbiturates do this (including the convulsant type) it is doubtful that this reaction is involved in the anesthetic effects of the barbiturates (255). Ramback and his coworkers have shown that pentobarbital will decrease ribose nucleic acid (RNA) turnover in spleen and marrow. A possible explanation of this effect is that ATP formation may be slowed down and thus decrease the rate of formation of RNA. This again may have nothing to do with the anesthetic effect of pentobarbital (256). Schulz & Goss have shown that menadione will uncouple phosphorylation *in vivo*. The gross symptoms of toxic manifestations of this drug are explained in this way (257). It has been suggested that the clinical symptoms of triethyl tin sulfate poisoning are due to uncoupling of phosphorylation. In a very thoughtful analysis of this problem, Aldridge & Cremer have attempted to suggest some of the consequences to a complex organism of a potent uncoupling agent (258). While it has been shown that many phenols and phenolic derivatives are capable of inhibiting oxidative phosphorylation, it should not be forgotten that they are capable of other actions as pointed out by Van Reen, who showed catalase to be inhibited by 2,4-dichlorophenol (259).

It will be assumed in this review that organic acids are anions in the tissues and therefore can act to displace other anions. Many or all acids introduced into the system may be activated as Co-A derivatives. A clear-cut example is to be found in the toxicity of fluoroacetic acid (FAc). Recent work

attests to the fact that FAc enters into the normal metabolic pathways of acetate and that it does not interfere directly with acetate metabolism but usually interferes with the body's metabolism at some later stage in the metabolism of acetate. In 1950, for example, Elliott & Kalnitsky reported that a fluorocitrate (FCit) was formed which competitively inhibited the oxidation of citrate (Cit) (260). These observations were fully verified by Busch & Potter (261). Lotspeich, Peters & Wilson showed that the conversion of Cit to isoCit by aconitase was competitively inhibited in both directions to an equal extent by FAc. However, the formation of Cit and isoCit from cisaconitate was less sensitive to this material (262). Peters & Wakelin (263) showed that convulsions in certain animals could be produced by intracranial injection of FCit. Marcus & Elliott have shown that FAc is activated just as acetate by the formation of a coenzyme A derivative. This material is fully active both in acetylation of amines and combination with oxaloacetate to form FCit (264). Brady has also studied fluoroacetyl Co-A (265). These then clearly indicate that the condensation to form a FCit need not necessarily be the only reactions of FAc, and indeed Phillips & Langdon showed that FAc was incorporated into the non-saponifiable fraction of rat liver lipides (266). Whether such a group of fluorinated materials could be toxic is certainly provocative.

Kandel & Chenoweth (267) have presented evidence to indicate that increased Cit levels in heart are not necessarily responsible for the interference with the electrocardiogram recordings, as high Cit levels can be obtained with fluorohexanoate administration without changes in the electrocardiogram.

On the other hand, the electroencephalogram in dogs correlated fairly well with the citrate levels on administration of FAc but not so well with fluorohexanoate. FAc produced extreme changes in the electrocardiogram in monkeys without producing elevation of the citrate content. On the other hand, in rats it was possible to prevent convulsions due to FAc with monoacetin, despite the fact that Cit accumulation occurred. These observations make it appear that Cit accumulation may not by itself account for the observed convulsive activities.

A possible way out of these difficulties is suggested by the results of Benitez, Pscheidt & Stone (268) who have shown a significant increase in brain ammonia content after poisoning animals with FAc. Ammonia can cause many of the typical convulsive activities which have been described for FAc poisoning. The problem which Benitez, *et al.* proposed to solve concerned the origin of the four carbon fragment from which the Cit is formed in the brain. They suggested that glutamate and aspartate upon deamination could lead to oxaloacetate formation and thereby increase the ammonia concentration in the brain. Furthermore, blockade of the Krebs cycle by FCit would effectively cut down the formation of high energy phosphate which would be needed for the fixation of ammonia into glutamate, glutamine, or protein. However, Dawson & Peters observed only very slight

changes in the phosphorous metabolism of brain (269). In fact, Awapara had observed earlier that aspartic acid, glutamic acid and glutamine concentrations were significantly lowered in liver, heart, and skeletal muscle by non-lethal doses of FAc (270) which would again suggest that ammonia formation may be responsible for the convulsive effects of FAc. A slightly altered viewpoint concerning the origin of the four carbon acid for formation of citrate could be that the four carbon acids may be formed by the malic enzyme which is known to be present in brain. However, Krebs & Davies (271) have shown that FCit inhibits the malic enzyme which would further bolster the argument that the four carbon acids came from glutamate or aspartic degradation.

Winter has shown that there is no effect of FAc on the intestinal absorption of glucose whereas glycine absorption is significantly diminished (272). In an elegant study of absorption phenomenon, Aldous & Rozee have shown that the absorption of FAc by yeast takes place only at pH's low enough for free FAc acid to be available to the cell. On the other hand, it would appear that the FAc ion is the toxic agent within the cell. Their studies further support the theory that the toxin to the yeast is actually a metabolite of FAc and not FAc itself. They present considerable discussion of the importance of the Krebs cycle in yeast (273).

Wort has speculated on the influence of 2,4-dichlorophenoxyacetic acid (2,4-D) in plants, pointing out that there is some evidence for induction of mitotic irregularities. He suggests that 2,4-D may influence genes in their activity of enzyme regulation. This may result in a decrease of B vitamins, which would be equivalent to a loss of hydrogen carriers, thus stimulating the production of side products which are plant toxins, for example, coumarin (274).

Thompson has attempted to discover the mechanism of the toxic action of ricin. Inhibition of fumarase was indicated, but the degree of inhibition was not great (275). Commercial pyruvic acid was shown to contain an inhibitor of α-ketoglutarate oxidase by Montgomery & Webb, the structure of which has been shown to be α-keto-γ-valerolactone-γ-carboxylic acid (276). Seevers, *et al.* were able to show that dehydroacetic acid inhibited the oxidation of succinate *in vitro*. This work is notable inasmuch as they were also able to demonstrate the *in vivo* inhibition of succinate oxidation by the demonstration of excess excretion of succinic acid in rats and dogs (277).

An interesting effect has been described by Cooper, Axelrod & Brodie in which a complex ester, β-diethylaminoethyl-α,α-diphenylhexanoate (SKF 525A) has been shown to block many of the pathways which are known to degrade various drugs, e.g., side chain oxidation of hexyl barbital and pentobarbital, dealkylation of N-ethyl and methyl amines, deamination of sympathomimetic amines, ether cleavage, and phenol conjugation. All these reactions have been shown to be retarded by this ester. Furthermore, these reactions have been shown to occur in liver microsomes and require reduced TPN and oxygen. Thus, this ester proves to be a potentiating drug for very

many different sorts of materials (278, 279). Brodie has reviewed much of this work concerning drug metabolism (280).

Two studies are worth noting as regards ability to alter the penetration of various materials. Grieg & Carter showed that physostigmine was able to increase the rate of entry of barbital into guinea pig brain slices. They suggest that physostigmine inhibited the cholinesterase of the brain tissue and that this resulted in the increased ability of the barbital to enter the tissue (281). Blakely & Boyer prepared the 6-fluoro analog of glucose and were able to show that the material inhibited the entry of glucose into rat diaphragm. This material was moderately toxic to mice but had no effect on virus growth in tissue cultures. It did markedly inhibit anerobic carbon dioxide production by yeast (282).

The interesting glucose analog, 2-deoxyglucose, has been described as inhibiting both aerobic and anaerobic glycolysis [Woodward & Hudson (283)]. Wick, Drury & Morita have shown that 2-deoxyglucose is transported into tissues and competitively inhibits glucose transfer and oxidation. These effects may last up to 8 hours (284).

Methodology

By means of the intravenous infusion of sodium succinate in man, Nordmann, *et al.* (285) were able to force an increased urinary elimination of succinic, fumaric, malic, citric, aconitic, and α-ketoglutaric acids as identified by paper chromatography. This approach would seem to have possibilities in the study of agents blocking the tricarboxylic acid cycle in intact animals. It could be extended to other metabolites quite easily. The trend toward multiple function recording produced an unique stationary manometric respirometer (286) for rat diaphragm together with very complete details for its construction and operation. The oxygen consumption, carbon dioxide production, cardiac output, electrocardiogram, and hemodynamic parameters may be determined on bullfrog heart according to the technique of Hashimoto, *et al.* (287). By using a calibrated glass hook inside a special respirometer flask, Ranson & Loomis (288) were able to obtain definite differences in the R.Q. of auricular muscle contracting under tension and without tension in the presence and absence of ouabain. Ingenious perfusion devices (289, 290, 291) warrant wide adoption. The ever-present problem of foaming has been partially controlled by a device described by Green, *et al.* (292) employing two chambers. Silicone antifoaming agents in aerosol spray containers are also helpful. To study the metabolism of isotopic lactate by the isolated dog heart, Cavert & Johnson made use of a number of useful approaches (293). The isolated lactating mammary gland has had extensive use in recent years and Linzell has commented on certain of its peculiarities as a method (294).

The use of tissue culture-techniques in pharmacology was the subject of a symposium (295). A new technique is described by Huston & Martin (296) in which the tissue under examination is placed upon fiber glass mats which

are attached to the side of a respirometer flask in the gaseous phase. This permits observations upon the oxygen consumption of tissues without dilution *in vitro* of a drug added *in vivo*. They have applied this technique to the effect of a variety of inhibitors on a variety of tissues and find that the effects of previously administered inhibitors on the respiration of subsequently isolated tissues are more pronounced when the tissues are placed on such glass mats in oxygen than when they are suspended in Krebs-Henseleit solution (297). The swelling of isolated tissues was shown to be caused by entry of isotonic bath media, not water alone. Sodium was found to accumulate intracellularly when metabolism was inhibited, according to Leaf (60). Liébecq offers a correction factor for glucose consumption by the isolated rat diaphragm (298) and the careful and unusual controls run by Klebanoff (299) revealed that increased oxygen consumption by liver tissue when alloxan was added to it arises nonenzymatically. Such effects may occur more often than realized while certain control observations reported in (286) bear examination by active workers in the field.

REVIEWS AND BOOKS

The collection of charts presented by Umbreit in 1952 under the title *Metabolic Maps* has been most helpful, but a second edition is needed (300). The review by Albert dealing with the influence of degree of ionization on drug action contributes toward fuller understanding of metabolic effects (301), while Friedenwald's review of histochemistry is particularly oriented in this direction (302). The Japanese literature is made available in English by Sato (303) in a report on the effect of autonomic drugs on animal metabolism. A review of the action of drugs on enzyme systems was presented by Quastel (304). The extensive review by Knox, Auerbach & Lin (305) of enzymatic and metabolic adaptations in mammals considers the effects of a number of drugs and hormones.

The review of James should be very useful to anyone concerned with the use of respiratory inhibitors (306). In a review of the structure activity relationships of plant growth regulators, Muir & Hansch point up the advantage of the use of kinetic analysis in the search for receptors and for knowledge of the nature of these materials (307). A thorough analysis of the effects of auxins has been given by Bonner & Bandurski (308).

LITERATURE CITED

1. Welch, A. D., and Bueding, E., "Biochemical Aspects of Pharmacology" In: *Currents in Biochemical Research*, 399–412 (Green, D. E., Ed., Interscience Publishers, Inc., New York, N. Y., 486 pp. (1946)
2. del Pozo, E. C., and Pardo, E. G., *J. Pharmacol. Exptl. Therap.*, **97**, 144–49 (1949)
3. Pardo, E. G., *J. Pharmacol. Exptl. Therap.*, **101**, 63–67 (1951)
4. Greiner, T., and Reilly, J., *Proc. Soc. Exptl. Biol. Med.*, **81**, 141–44 (1952)
5. Fischer, C. S., Sjoerdsma, A., and Johnson, G. R., *Circulation*, **5**, 496–503 (1952)

6. Kuschinsky, G., Lange, G., Scholtissek, C., and Turba, F., *Biochem. Z.* **327,** 314–30 (1955)
7. Wollenberger, A., *Pharmacol. Revs.*, **1,** 311–52 (1949)
8. Bing, R. J., *Circulation*, **12,** 635–47 (1955)
9. Olson, R. E., *Am. J. Med.*, **20,** 159–62 (1956)
10. Merlen, J. F., *Ann. biol. clin.*, **13,** 369–78 (1955)
11. Wilbrandt, W., *Schweiz. med. Wochshr.*, **85,** 315–20 (1955)
12. Loubatières, A., *Actualités Pharmacol.*, **3,** 69–103 (1951)
13. Loubatières, A., *J. physiol.* (Paris), **43,** 517–79 (1951)
14. Greiner, T., *J. Pharmacol. Exptl. Therap.*, **105,** 178–95 (1952)
15. Wollenberger, A., and Karsh, M. L., *J. Pharmacol. Exptl. Therap.*, **105,** 477–85 (1952)
16. Gruhzit, C. C., and Farah, H. E., *J. Pharmacol. Exptl. Therap.*, **114,** 335–43 (1955)
17. Rothlin, E., Toeschler, M., and Cerletti, A., *Circulation Research*, **3,** 32–38 (1955)
18. Köhler, V., Loll, H., and Schroër, H., *Z. biol.*, **107,** 209–11 (1954)
19. Ellis, S., *J. Pharmacol. Exptl. Therap.*, **105,** 381–90 (1952)
20. Ellis, S., *J. Pharmacol. Exptl. Therap.*, **109,** 233–43 (1953).
21. Lee, K. S., *J. Pharmacol. Exptl. Therap.*, **109,** 304–12 (1953)
22. Lee, K. S., *J. Pharmacol. Exptl. Therap.*, **112,** 484–94 (1954)
23. Bertelli, A., and Musseni, E., *Boll. soc. ital. biol. sper.*, **31,** 1168–71 (1955)
24. Lee, K. S., *J. Pharmacol. Exptl. Therap.*, **109,** 313–17 (1953)
25. Price, H. L., and Helrich, M., *J. Pharmacol. Exptl. Therap.*, **115,** 206–16 (1955)
26. Bennett, D. R., *An Analysis of the Papillary Muscle as a Cardiotonic Screening Method* (Doctoral Thesis, Univ. of Michigan, Ann Arbor, Mich., 1956)
27. Chenoweth, M. B., and Koelle, E. S., *J. Lab. Clin. Med.*, **31,** 600–08 (1946)
28. Gardner, E. A., Wilson, M., and Farah, A., *J. Pharmacol. Exptl. Therap.*, **110,** 166–79 (1954)
29. Gardner, E. A., and Farah, A., *J. Pharmacol. Exptl. Therap.*, **111,** 255–64 (1954)
30. Giotti, A., and Buffoni, N. F., *Arch. ital. sci. farmacol.*, **5,** 271–84 (1955)
31. Ransom, V. R., and Loomis, T. A., *J. Pharmacol. Exptl. Therap.*, **104,** 219–23 (1952)
32. Webb, J. L., *Brit. J. Pharmacol.*, **5,** 87–117 (1950)
33. Fischer, H., Huber, P., and Langemann, M., *Helv. Physiol. et Pharmacol. Acto*, **9,** 416–37 (1951)
34. Doull, J., Herrmann, R. G., Geiling, E. M. K., and DuBois, K. P., *Arch. intern. pharmacodynamie*, **86,** 487–96 (1951)
35. Herrmann, R. G., Flamboe, G. E., and Chen, K. K., *J. Pharmacol. Exptl. Therap.*, **112,** 23–28 (1954)
36. Nisada, S., and Nakashima, T., *Nagoya Med. J.*, **1,** 277–89 (1953)
37. Langemann, M., Brody, T. M., and Bain, J. A., *J. Pharmacol. Exptl. Therap.*, **108,** 274–80 (1953)
38. Smith, J. A., Glassman, M., Lind, A. H., Post, M., Sonn, H., and Warren, S., *Proc. Soc. Exptl. Biol. Med.*, **86,** 747–49 (1954)
39. Reiter, M., and Barron, E. S. G., *Arch. exptl. Pathol. Pharmakol.*, **214,** 341–48 (1952)
40. Hasselbach, W., and Weber, A., *Pharmacol. Revs.*, **7,** 97–117 (1955)
41. Perry, S. V., *Physiol. Revs.*, **36,** 1–76 (1956)

42. Morales, M. F., Botts, J., Blum, J. J., and Hill, T. L., *Physiol. Revs.*, **35,** 475–505 (1955)
43. Wollenberger, A., *Experientia*, **10,** 311–12 (1954)
44. Fawaz, G., and Hawa, E. S., *Proc. Soc. Exptl. Biol. Med.*, **84,** 277–80 (1953)
45. Brody, T. M., Palmer, J. F., and Bennett, D. R., *Proc. Soc. Exptl. Biol. Med.*, **86,** 739–41 (1954)
46. Fawaz, G., *Arch. exptl. Pathol. Pharmakol.*, **228,** 377–86 (1956)
47. Harvey, S. C., *Am. J. Physiol.*, **183,** 559–64 (1955)
48. Lorber, V., *Circulation Research*, **1,** 298–311 (1953)
49. Berman, D. A., and Saunders, P. R., *Circulation Research*, **3,** 559–63 (1955)
50. Masuoka, D. T., Berman, D. A., and Saunders, P. R., *Am. J. Physiol.*, **170,** 301 (1952)
51. Sutherland, G. B., *Stanford Univ. Dissertation Abstracts*, **14,** 546 (1954)
52. Blain, J. M., Eddleman, E. E., Siegel, A., and Bing, R. J., *J. Clin. Invest.*, **25,** 314–21 (1956)
53. Gonlubol, F., Siegel, A., and Bing, R. J., *Circulation Research*, **4,** 298–301 (1956)
54. Wolfson, S. K., and Ellis, S., *Proc. Soc. Exptl. Biol. Med.*, **91,** 226–28 (1956)
55. Zwemer, R. L., Pines, K. L., Lowenstein, B. E., *Science*, **91,** 600–02 (1940)
56. Weidmann, S., *J. Physiol.*, **127,** 213–24 (1955)
57. Kahn, J. B., and Acheson, G. B., *J. Pharmacol. Exptl. Therap.*, **115,** 305–18 (1955)
58. Reiter, M., *Arch. exptl. Pathol. Pharmakol.*, **227,** 300–15 (1956)
59. Tanz, R. D., Clark, G. M., and Whitehead, R. W., *Proc. Soc. Exptl. Biol. Med.*, **92,** 167–69 (1956)
60. Leaf, A., *Biochem. J.* (*London*), **62,** 241–48 (1956)
61. Webb, T. L., Saunders, P. R., and Nakamura, K., *J. Pharmacol. Exptl. Therap.*, **101,** 287–95 (1951)
62. Lee, K. S., *Proc. Soc. Exptl. Biol. Med.*, **86,** 444–46 (1954)
63. Porro, A., *Arch. sci. biol.* (*Italy*), **39,** 416–23 (1955)
64. Lüllmann, H., *Arch. für Kreislaufforsch.*, **23,** 12–76 (1955)
65. Giotti, A., *Arch. ital. sci. farmacol.*, **6,** 83–207 (1956)
66. Ferguson, F. C., *J. Pharmacol. Exptl. Therap.*, **108,** 186–200 (1953)
67. Schatzmann, H. J., and Witt, P. N., *J. Pharmacol. Exptl. Therap.*, **112,** 501–08 (1954)
68. Ellis, S., and Beckett, S. B., *J. Pharmacol. Exptl. Therap.*, **112,** 202–09 (1954)
69. Ellis, S., Davis, A. H., and Anderson, H. L., *J. Pharmacol. Exptl. Therap.*, **115,** 120–25 (1955)
70. Haft, D. E., and Mirsky, I. A., *J. Pharmacol. Exptl. Therap.*, **105,** 74–79 (1952)
71. Crepax, P., and Fadiga, E., *Arch. fisiol.*, **54,** 330–43 (1955)
72. Fleckenstein, A., Janke, J., Kruse, R., and Lechner, G., *Arch. exptl. Pathol. Pharmakol.*, **224,** 465–75 (1955)
73. Hermans, N., *Arch. intern. physiol. biochem.*, **64,** 251–68 (1956)
74. Butler, T. C., *Pharmacol. Revs.*, **2,** 121–60 (1950)
75. Levy, L., and Featherstone, R. M., *J. Pharmacol. Exptl. Therap.*, **110,** 221–25 (1954)
76. Hunter, F. E., and Lowry, O. H., *Pharmacol. Revs.*, **8,** 89–135 (1956)
77. Brody, T. M., and Bain, J. A., *J. Pharmacol. Exptl. Therap.*, **110,** 148–55 (1954)
78. Quastel, J. H., *Proc. 3rd International Congress Biochemistry*, 496–504 (Academic Press, New York, N. Y., 544 pp., 1956)

79. Rosenberg, A. J., *Proc. 3rd International Congress Biochemistry*, 504–07 (Academic Press, New York, N. Y., 544 pp., 1956)
80. Grenell, R. G., *Proc. 3rd International Congress Biochemistry*, 509–10 (Academic Press, New York, N. Y., 544 pp., 1956)
81. Finkelstein, M., Spencer, W. A., and Ridgeway, E. R., *Proc. Soc. Exptl. Biol. Med.*, **87**, 343–44 (1954)
82. Gänshirt, H., and Brilmayer, H., *Arch. intern. pharmacodynamie*, **98**, 467–74 (1954)
83. Abood, L. G., *Proc. Soc. Exptl. Biol. Med.*, **88**, 688–90 (1955)
84. Grenell, R. G., Mendelson, J., and McElroy, W. D., *Arch. Neurol. Psychiat.*, **73**, 347–51 (1955)
85. Yagi, K., Nagatsu, T., and Ozawa, T., *Nature*, **177**, 891–92 (1956)
86. Century, B., and Horwitt, M. K., *Proc. Soc. Exptl. Biol. Med.*, **91**, 493–96 (1956)
87. Bernsohn, J., Namajuska, I., and Cochrane, L. S. G., *Proc. Soc. Exptl. Biol. Med.*, **92**, 201–03 (1956)
88. Sutherland, V. C., Hine, C. H., and Burbridge, T. W., *J. Pharmacol. Exptl. Therap.*, **116**, 469–79 (1956)
89. Hendershot, L. C., and Chenoweth, M. B., *J. Pharmacol. Exptl. Therap.*, **113**, 160–68 (1955)
90. Kristiansen, K., and Courtois, G., *Electroencephalog. Clin. Neurophysiol.*, **1**, 265–72 (1949)
91. Shideman, F. E., and Seevers, M. H., *Proc. Soc. Exptl. Biol. Med.*, **82**, 63–64 (1953)
92. Chance, M. R. A., *Brit. J. Pharmacol.*, **6**, 1–7 (1951)
93. Brierley, J. B., and McCoubrey, A., *Brit. J. Pharmacol.*, **8**, 366–70 (1953)
94. Neufeld, H. A., Greenberg, L. J., and Slater, I. H., *J. Pharmacol. Exptl. Therap.*, **113**, 292–98 (1955)
95. Mayer, S. E., and Bain, J. A., *J. Pharmacol. Exptl. Therap.*, **111**, 210–23 (1954)
96. Shulman, A., *Nature*, **177**, 703 (1956)
97. Dessauer, H. C., and Brazda, F. G., *Proc. Soc. Exptl. Biol. Med.*, **89**, 676–78 (1955)
98. Shintani, S., *J. Pharmacol. Soc. Japan*, **76**, 13–15 (1956)
99. Pfeiffer, C. C., Jenney, E. H., and Marshall, W. H., *Electroencephalog. Clin. Neurophysiol.*, **8**, 307–15 (1956)
100. Annau, E., *Can. J. Biochem. Physiol.*, **33**, 833–38 (1955)
101. Abood, L. G., Kun, E., and Geiling, E. M. K., *J. Pharmacol. Exptl. Therap.*, **98**, 373–79 (1950)
102. Wang, R. I. H., and Bain, J. A., *J. Pharmacol. Exptl. Therap.*, **108**, 349–53 (1953)
103. Wang, R. I. H., and Bain, J. A., *J. Pharmacol. Exptl. Therap.*, **108**, 354–61 (1953)
104. Millichap, J. G., Woodbury, D. M., and Goodman, L. S., *J. Pharmacol. Exptl. Therap.*, **115**, 251–58 (1955)
105. Woodbury, D. M., *J. Pharmacol. Exptl. Therap.*, **115**, 74–94 (1955)
106. Toman, J. E. P., and Taylor, J. D., *Epilepsia*, **1**, 31–48 (1952)
107. Richards, R. K., and Taylor, J. D., *Anesthesiology*, **17**, 414–58 (1956)
108. McIlwain, M., *Biochemistry and the Central Nervous System* (Little, Brown and Company, Boston, Mass., 272 pp., 1955)
109. Elliott, K. A. C., *Research Pubs. Assoc. Research Nervous Mental Disease*, **32**, 422–31 (1953)

110. Woelsch, H. (ed.), *Proc. 1st Intern. Neurochem. Symposium* (Academic Press, Inc., New York, N. Y., 537 pp., 1955)
111. Richter, M. L., *J. Pharmacol. Exptl. Therap.*, **102**, 94–96 (1951)
112. Hove, E. L., and Hardin, J. O., *J. Pharmacol. Exptl. Therap.*, **106**, 88–93 (1952)
113. Villela, G. G., and Mitidieri, E., *Nature*, **175**, 208–09 (1955)
114. Affonso, O. R., *Proc. Soc. Exptl. Biol. Med.*, **90**, 527–29 (1955)
115. Thomson, J. F., and Moss, E. M., *Cancer*, **8**, 789–95 (1955)
116. Eden, E., and Harrison, D. D., *Australian J. Exptl. Biol. Med. Sci.*, **33**, 85–90 (1955)
117. Bruns, F., and Neuhaus, J., *Biochem. Z.*, **326**, 242–51 (1955)
118. Brauer, R. W., *Ann. Rev. Physiol.*, **18**, 253–78 (1956)
119. Brauer, R. W., and Pessotti, R. L., *J. Pharmacol. Exptl. Therap.*, **97**, 358–70 (1949)
120. Young, M. K., Jr., Prudden, J. F., and Stirman, J. A., *J. Lab. Clin. Med.*, **46**, 155–66 (1955)
121. Miller, L. L., and Axelrod, L. R., *Metabolism*, **3**, 438–48 (1954)
122. Axelrod, L. R., and Miller, L. L., *Arch. Biochem. and Biophys.*, **60**, 373–78 (1956)
123. Goldner, M. G., and Jauregui, R. H., *Proc. Soc. Exptl. Biol. Med.*, **84**, 116–20 (1953)
124. Bass, A. D., Diermeier, H. F., DiStefano, H. S., and Cafruny, E. J., *J. Pharmacol. Exptl. Therap.*, **107**, 478–81 (1953)
125. Schmid, R., Figen, J. F., and Schwartz, S., *J. Biol. Chem.*, **217**, 263–67 (1955)
126. Handley, C. A., and Lavik, P. S., *J. Pharmacol. Exptl. Therap.*, **100**, 115–18 (1950)
127. Farah, A., Cafruny, E. J., and DiStefano, H. S., *J. Histochem. and Cytochem.*, **3**, 271–73 (1955)
128. Ruskin, A., and Ruskin, B., *J. Pharmacol. Exptl. Therap.*, **107**, 325–31 (1953)
129. Fawaz, G., and Fawaz, E. N., *Proc. Soc. Exptl. Biol. Med.*, **87**, 30–34 (1954)
130. DeGroot, C. A., and Weber, J. F., *Acta Physiol. Pharmacol. Neerl.*, **4**, 371–77 (1955)
131. Farah, A., Graham, G., and Koda, F., *J. Pharmacol. Exptl. Therap.*, **108**, 410–23 (1953)
132. Graham, G., Koda, F., and Farah, A., *Proc. Soc. Exptl. Biol. Med.*, **84**, 226–28 (1953)
133. Cross, R. J., and Taggart, J. V., *Am. J. Physiol.*, **161**, 181–90 (1950)
134. Dominguez, A. M., and Shideman, F. E., *Proc. Soc. Exptl. Biol. Med.*, **90**, 329–32 (1955)
135. Dominguez, A., *Mode of Action of Various Metabolic Inhibitors* (Doctoral Thesis, Univ. of Wisconsin, Madison, Wis., 1956)
136. Schwalb, H., Bauernfeind, A., and Hensel, H., *Arch. exptl. Pathol. Pharmakol.*, **224**, 285–94 (1955)
137. Newton, B. A., *Bacteriol. Revs.*, **20**, 14–27 (1956)
138. Cooper, P. D., *Bacteriol. Revs.*, **20**, 28–48 (1956)
139. Umbreit, W. W., *Pharmacol. Revs.*, **5**, 275–84 (1953)
140. Umbreit, W. W., *Am. J. Med.*, **18**, 717–22 (1955)
141. Binkley, S. B., *Ann. Rev. Biochem.*, **24**, 597–626 (1955)
142. Matthews, R. E. F., and Smith, J. O., *Advances in Virus Research, III*, 51–148 (Academic Press, Inc., New York, N. Y., 339 pp., 1955)
143. Julius, H. W., *Ann. Rev. Microbiol.*, **6**, 411–36 (1952)

144. Umbriet, W. W., *Ann. Rev. Microbiol.*, **8,** 167–80 (1954)
145. Macheboeuf, M., *Actualités Pharmacol.*, **2,** 111–22 (1950)
146. Chenoweth, M. B., *Pharmacol. Revs.*, **8,** 57–87 (1956)
147. Gangadharam, P. R. J., and Sirse, M., *Current Sci.* (India), **24,** 243–44 (1955)
148. Knox, R., Albert, A., and Rees, C. W., *Nature*, **175,** 1085–86 (1955)
149. Lichstein, H. C., *Proc. Soc. Exptl. Biol. Med.*, **88,** 519–22 (1955)
150. Davison, A. N., *Bichim. et Biophys. Acta*, **19,** 131–40 (1956)
151. Zbinden, G., and Studer, A., *Z. Tuberk.* **107,** 97–107 (1955)
152. Zeller, E. A., and Barsky, J., *Proc. Soc. Exptl. Biol. Med.*, **81,** 459–61 (1952)
153. Griesemer, E. C., and Wells, J. A., *J. Pharmacol. Exptl. Therap.*, **116,** 282–86 (1956)
154. Gonnard, P., and Glikman, G., *Bull. soc. chim. biol.*, **37,** 501–10 (1955)
155. Cymerman-Craig, J., Rubbo, S. D., and Pierson, B. J., *Brit. J. Exptl. Pathol.*, **36,** 254–60 (1955)
156. Abood, L. G., and Gerard, R. W., *J. Pharmacol. Exptl. Therap.*, **108,** 261–73 (1953)
157. Bernheim, F., and DeTurk, W. E., *J. Pharmacol. Exptl. Therap.*, **116,** 387–93 (1956)
158. Cymerman-Craig, J., Rubbo, S. D., Loder, J. W., and Pierson, B. J., *Brit. J. Exptl. Pathol.*, **36,** 261–67 (1955)
159. Gould, B. S., Frigerio, N. A., and Lebowitz, W. B., *Arch. Biochem.*, **56,** 476–86 (1955)
160. Gould, B. S., Bosniak, M. A., Neidleman, S., and Gatt, S., *Arch. Biochem.*, **44,** 284–97 (1953)
161. Mazia, D., *Advances in Biol. and Med. Phys.*, **4,** 70–118 (1956)
162. Clowes, G. H. A., *Ann. N. Y. Acad. Sci.*, **51,** 1409–31 (1951)
163. Biesele, J. J., Berger, R. E., Clarke, M., and Weiss, L., *Exptl. Cell Research*, Suppl. **2,** 279–303 (1952)
164. Hitchings, G. H., and Elion, G. B., *Proc. 3rd International Congress Biochemistry*, 55–61 (Academic Press, Inc., New York, N. Y., 544 pp., 1956)
165. Brown, G. B., *Proc. 3rd International Congress Biochemistry*, 61–63 (Academic Press, Inc., New York, N. Y., 544 pp., 1955)
166. Cornman, I., *Intern. Rev. of Cytol.*, **3,** 113–30 (1954)
167. Skipper, H. E., Schabel, F. M., Jr., Binns, V., Thomson, J. R., Wheeler, G. P., *Cancer Research*, **15,** 143–46 (1955)
168. Vicino, N., *Fisol. e med.* (Rome), **18,** 263–69 (1954)
169. Siegel, B. V., and Cailleau, R., *Arch. Biochem. and Biophys.*, **60,** 506–08 (1956)
170. Clowes, G. H. A., and Keltch, A. K., *Proc. Soc. Exptl. Biol. Med.*, **81,** 356–62 (1952)
171. Featherstone, R. M., Nelson, W. D., Welden, F., Marberger, E., Boccabella, A., and Boccabella, R., *Endocrinology*, **56,** 727–36 (1955)
172. Wolf, G., *Chemical Induction of Cancer* (Harvard Univ. Press, Cambridge, Mass., 250 pp., 1952)
173. Alexander, P., *Advances in Cancer Research*, **2,** 1–72 (1954)
174. Miller, J. A., and Miller, E. C., *Advances in Cancer Research*, **1,** 340–96 (1953)
175. Ross, W. C. J., *Advances in Cancer Research*, **1,** 397–451 (1953)
176. Haddow, A., *Ann. Rev. Biochem.*, **24,** 689–742 (1955)
177. Badger, G. M., *Advances in Cancer Research*, **2,** 73–127 (1954)
178. Hechter, O., *Vitamins and Hormones*, **13,** 293–346 (1955)

179. Roberts, S., and Szego, C. M., *Physiol. Revs.*, **33,** 593–629 (1953)
180. Levine, R., and Goldstein, M. S., *Recent Progr. in Hormone Research*, **11,** 343–80 (1955)
181. Stadie, W. C., *Physiol. Revs.*, **34,** 52–100 (1954)
182. Young, F. C., *Proc. 3rd International Congress Biochemistry*, 329–31 (Academic Press, New York, N. Y., 544 pp., 1956)
183. Sarzana, G., Rubino, F., and Cascio, G., *Arch. fisiol.*, **53,** 200–32 (1935)
184. Vanderlaan, W. P., and Storrie, U. M., *Pharmacol. Revs.*, **7,** 301–34 (1955)
185. Gorbman, A., *Physiol. Revs.*, **35,** 336–46 (1955)
186. Selenkow, H. A., and Asper, S. P., *Physiol. Revs.*, **32,** 426–74 (1955)
187. Roche, J., and Michel, R., *Physiol. Revs.*, **35,** 583–610 (1955)
188. Roche, J., and Michel, R., *Ann. Rev. Biochem.*, **23,** 481–500 (1954)
189. Pitt-Rivers, R., *Proc. 3rd International Congress Biochemistry*, 331–33 (Academic Press, New York, N. Y., 544 pp., 1956)
190. Olson, R. A., *Physiol. Revs.*, **35,** 57–90 (1955)
191. Lardy, H., *Brookhaven Symposia in Biology*, **7,** 90–101 (Brookhaven National Laboratories, Upton, N.Y., 1955)
192. Staehelin, M., *Helv. Physiol. et Pharmacol. Acta*, **13,** 50–59 (1955)
193. Tapley, D. F., Cooper, C., and Lehninger, A. L., *Bichim. et Biophys. Acta*, **18,** 597–98 (1955)
194. Hoch, F. L., and Lipmann, M., *Proc. Natl. Acad. Sci. U.S.*, **40,** 909–21 (1954)
195. Mudd, S., Harvey, J. H. P., and Lipmann, F., *Proc. Natl. Acad. Sci. U.S.*, **41,** 571–76 (1955)
196. Martius, C., *Proc. 3rd International Congress Biochemistry*, 1–9 (Academic Press, New York, N.Y., 544 pp., 1956)
197. Fraser, R., Hanno, M. G. W., and Pitney, W. R., *Brit. J. Pharmacol.*, **10,** 1–6 (1955)
198. Sekizawa, Y., *J. Biochem. (Japan)*, **42,** 217–19 (1955)
199. Hung, L. V., and Delost, P., *Arch. Sci. Physiol.*, **6,** 381–89 (1952)
200. Peeters, G., Coussens, R., and Sierens, G., *Arch. intern. pharmacodynamie*, **96,** 62–75 (1953)
201. Scalabrino, R., and Rossanda, M., *Boll. soc. ital. biol. sper.*, **30,** 1374–76 (1954)
202. Ganis, F. M., Axelrod, L. R., and Miller, L. L., *J. Biol. Chem.*, **218,** 841–48 (1956)
203. Ozawa, G., Beaton, J. R., and McHenry, E. W., *Proc. Soc. Exptl. Biol. Med.*, **83,** 781–84 (1953)
204. Levey, H. A., *Proc. Soc. Exptl. Biol. Med.*, **82,** 177–80 (1953)
205. Villee, C. A., and Gordon, E. E., *J. Biol. Chem.*, **261,** 203–14 (1955)
206. Mueller, G. C., and Herranen, A., *J. Biol. Chem.*, **219,** 585–94 (1956)
207. Nachmanson, D., and Wilson, I. B., *Advances in Enzymology*, **12,** 259–339 (Interscience Publishers, Inc., New York, N. Y., 570 pp. 1951)
208. Swain, G. G., Brown, J. F., Jr., *J. Am. Chem. Soc.*, **74,** 2538–43 (1952)
209. McCarthy, J. F., Green, L. F., and King, C. G., *J. Biol. Chem.*, **128,** 455–62 (1939)
210. Dagliesh, C. E., *Arch. Biochem. and Biophys.*, **58,** 214–26 (1955)
211. Udenfriend, S., Clark, C. T., Axelrod, J., and Brodie, B. B., *J. Biol. Chem.*, **208,** 741–50 (1956)
212. Udenfriend, S., Clark, C. T., Axelrod, J., and Brodie, B. B., *J. Biol. Chem.*, **208,** 731–40 (1956)

213. Kaplan, N. O., Enzymes: *Units of Biological Structure and Function*, 172–73 (Academic Press Inc., New York, N. Y., 624 pp. 1956)
214. Bergmann, F., and Segal, R., *Bichim. et Biophys. Acta*, **16**, 513–19 (1955)
215. Paulescu, F., Vargiu, L., and Gibertoni, G., *Arch. intern. pharmacodynamie*, **104**, 11–18 (1955)
216. Mitidieri, E., Ribeiro, L. P., Affonso, O. R., and Villela, G. G., *Bichim. et Biophys. Acta*, **17**, 587 (1955)
217. Bensuson, H. B., Derow, M. A., and Walker, B. S., *Arch. Biochem. and Biophys.*, **49**, 293–302 (1954)
218. Laidler, K. J., *Introduction to The Chemistry of Enzymes.*, 14–33 (McGraw-Hill Book Co., Inc., New York, N. Y., 208 pp. 1954)
219. Lineweaver, H., and Burke, D., *J. Am. Chem. Soc.*, **56**, 658–66 (1934)
220. Massart, L., *The Enzymes*, **I**, 307–42 (Academic Press Inc., New York, N. Y., 724 pp. 1950)
221. Sumner, J. B., and Somers, F., *Chemistry and Methods of Enzymes*, 41–50 (Academic Press, Inc., New York, N. Y., 462 pp. 1953)
222. DuBois, K. P., Peterson, D. F., and Zins, G. R., *Proc. Soc. Exptl. Biol. Med.*, **91**, 244–48 (1956)
223. DuBois, K. P., Deroin, J. and Cochran, K. W., *Proc. Soc. Exptl. Biol. Med.* **81**, 230–34 (1952)
224. Miller, Z., *Proc. Soc. Exptl. Biol. Med.*, **87**, 170–71 (1954)
225. Gawron, O., Deil, J., and Glaid, A. J., 3rd. *Biochim. et Biophys. Acta*, **19**, 170–71 (1956)
226. Wood, J. L., and Cooley, S. L., *J. Biol. Chem.* **218**, 449–57 (1956)
227. Kamijo, K., and Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **105**, 349–57 (1952)
228. Admiral, J., Myers, D. K., and van Houten, J. C., *Nature*, **176**, 468–69 (1955)
229. Murtha, E. F., McNamara, B. P., Edberg, L. J., Bergner, A. D., and Wills, J. H., *J. Pharmacol. Exptl. Therap.*, **115**, 291–99 (1955)
230. Strickland, K. P., and Thompson, R. H. S., *Biochem. J. (London)*, **60**, 468–75 (1955)
231. Hokin, L. E., and Hokin, M. R., *Bichim. et Biophys. Acta*, **16**, 229–37 (1955)
232. Wheeler, G. P., Morrow, J. S., and Skipper, H. E., *Arch. Biochem. and Biophys.*, **57**, 124–31 (1955)
233. Wheeler, G. P., Morrow, J. S., and Skipper, H. E., *Arch. Biochem. and Biophys.*, **57**, 132–39 (1955)
234. Gemmill, C. L., and Bowman, E. M., *J. Pharmacol. Exptl. Therap.*, **100**, 244–49 (1950)
235. Sizer, I. W., *J. Gen. Physiol.*, **25**, 399–409 (1942)
236. Davenport, M. W., Chavré, V. J., and Davenport, V. D., *Am. J. Physiol.*, **184**, 1–10 (1956)
237. Frieden, E., and Naile, B., *Arch. Biochem. and Biophys.*, **48**, 448–57 (1954)
238. Yall, I., and Green, M. N., *Proc. Soc. Exptl. Biol. Med.*, **79**, 306–08 (1952)
239. Cavanaugh, D. J., Harris, J., and Hearon, J. Z., *J. Am. Chem. Soc.* **77**, 1531–35 (1955)
240. Kewitz, H., and Wilson, I. B., *Arch. Biochem. and Biophys.*, **60**, 261–62 (1956)
241. Roy, B. B., and Kuperman, A. S., *Proc. Soc. Exptl. Biol. Med.*, **89**, 255–58 (1955)
242. Kaplan, N. O., *A. Symposium on Phosphorus Metabolism*, 428–436 (Johns Hopkins Press, Baltimore, Md., 1951)

243. Greville, G. D., and Needham, D. M., *Bichim. et Biophys. Acta*, **16**, 284–85 (1955)
244. Koscak, M., *Acta Biochem. and Biophys.* **52**, 485–87 (1954)
245. Chappell, J. B., and Perry, S. V., *Bichim. et Biophys. Acta*, **16**, 285–87 (1955)
246. Slater, E. C., and Lewis, S. E., *Biochem. J.* (*London*), **58**, 337–44 (1954)
247. Cohn, M., *A Symposium on Phosphorus Metabolism*, 374–76 (Johns Hopkins Press, Baltimore, Md., 1951)
248. Grisolía, S., *Bichim. et Biophys. Acta*, **18**, 437–38 (1955)
249. Aisenberg, A. C., and Potter, V. R., *J. Biol. Chem.*, **215**, 737–49 (1955)
250. Rolinson, G. N., *J. Gen. Microbiol.*, **11**, 412–19 (1954)
251. Born, G. V. R., Bülbring, E., *J. Physiol.* (London), **127**, 626–35 (1955)
252. Schacter, B., *Arch. Biochem. and Biophys.*, **57**, 387–400 (1955)
253. Brody, T. M., *Pharmacol. Revs.*, **7**, 335–63 (1955)
254. Bostroem, H., and Mansson, B., *J. Pharm. Pharmacol.*, **7**, 185–90 (1955)
255. Marks, B. H., *Science*, **123**, 332–33 (1956)
256. Ramback, W. A., Moomaw, D. R., Alt, H. L., and Cooper, J. A. D., *Proc. Soc. Exptl. Biol. Med.*, **79**, 59 (1952)
257. Schulz, A. R., and Goss, H., *Bichim. et Biophys. Acta*, **20**, 443–44 (1956)
258. Aldridge, W. N., and Cremer, J. E., *Biochem. J.* (*London*), **61**, 406–18 (1955)
259. Van Reen, R., *Arch. Biochem. and Biophys.*, **50**, 219–21 (1954)
260. Elliott, W. B., and Kalnitsky, G., *J. Biol. Chem.*, **186**, 487–93 (1950)
261. Busch, H., and Potter, V. R., *Proc. Soc. Exptl. Biol. Med.*, **81**, 172–75 (1952)
262. Lotspeich, W. D., Peters, R. A., and Wilson, T. H., *Biochem. J.* (*London*), **51**, 20–25 (1952)
263. Peters, R. A., and Wakelin, R. W., *J. Physiol.* (*London*), **119**, 421–27 (1953)
264. Marcus, A., and Elliott, W. B., *J. Biol. Chem.*, **218**, 823–30 (1956)
265. Brady, R. O., *J. Biol. Chem.*, **217**, 213–44 (1955)
266. Phillips, A. H., and Langdon, R. G., *Arch. Biochem. and Biophys.*, **58**, 247–49 (1955)
267. Kandel, A., and Chenoweth, M. B., *J. Pharmacol. Exptl. Therap.*, **104**, 234–47 (1952)
268. Benitez, D., Pscheidt, G. R., and Stone, W. E., *Am. J. Physiol.*, **176**, 488–92 (1954)
269. Dawson, R. M. C., and Peters, R. A., *Bichim. et Biophys. Acta*, **16**, 254–57 (1955)
270. Awapara, J., *J. Biol. Chem.* **197**, 695–99 (1952)
271. Krebs, A. A., and Davies, D. D., *Arch. sci. biol.*, **39**, 533–38 (1955)
272. Winter, M., *Acta Physiol. Acad. Sci. Hung.* **4**, 91–95 (1953)
273. Aldous, J. G., and Rozee, K. R., *Biochem. J.* (*London*), **62**, 605–10 (1956)
274. Wort, D. J., *Weeds*, **3**, 131–35 (1954)
275. Thomson, J. F., *J. Pharmacol. Exptl. Therap.*, **100**, 370–81 (1950)
276. Montgomery, C. H., and Webb, L. J., *Science*, **120**, 843–44 (1954)
277. Seevers, M. H., Shideman, F. E., Woods, L. A., Weeks, J. R., and Kruse, W. T., *J. Pharmacol. Exptl. Therap.*, **99**, 69–83 (1950)
278. Cooper, J. R., Axelrod, J., and Brodie, B. B., *J. Pharmacol. Exptl. Therap.*, **112**, 55–63 (1954)
279. Axelrod, J., Reichenthal, J., and Brodie, B. B., *J. Pharmacol. Exptl. Therap.*, **112**, 49–54 (1954)
280. Brodie, B. B., *J. Pharm. and Pharmacol.*, **8**, 1–17 (1956)
281. Grieg, M. E., and Carter, M. K., *Arch. Biochem. and Biophys.*, **52**, 175–79 (1954)

282. Blakeley, E. R., and Boyer, P. D., *Bichim. et Biophys. Acta*, **16**, 576–82 (1955)
283. Woodward, G. E., and Hudson, M. T., *Cancer Research*, **14**, 599–605 (1954)
284. Wick, A. N., Drury, D. R., and Morita, T. N., *Proc. Soc. Exptl. Biol. Med.*, **89**, 579–82 (1955)
285. Nordmann, J., Nordmann, R., Gauchery, O., Marty, A., and Du Ruisseau, J. P., *Bull. soc. chim. biol.*, **37**, 325–30 (1955)
286. Weeks, J. R., and Chenoweth, M. B., *J. Pharmacol. Exptl. Therap.* **104**, 187–201 (1952)
287. Hashimoto, K., Nukada, H., and Morita, T., *Folia Pharmacol. Japon.*, **50**, 137–42 (1954)
288. Ranson, V. R., and Loomis, T. A., *J. Pharmacol. Exptl. Therap.*, **104**, 219–23 (1952)
289. Long, J. A., and Lyons, W. R., *J. Lab. Clin. Med.*, **44**, 614–26 (1954)
290. Clarke, E. W., *J. Physiol.* (London), **129**, 37P (1955)
291. Meli, A., and Capraro, V., *Boll. soc. ital. biol. sper.*, **30**, 1415–17 (1954)
292. Green, J. P., Riley, J. A., and White, J. M., *Rev. Sci. Instruments*, **24**, 183–84 (1953)
293. Cavert, H. M., and Johnson, J. A., *Am. J. Physiol.*, **184**, 575–81 (1956)
294. Linzell, J. J., *Rev. can. biol.*, **13**, 291–98 (1954)
295. Symposium, *Ann. N. Y. Acad. Sci.*, **58**, 971–1326 (1954)
296. Huston, M. J., and Martin, A. W., *Proc. Soc. Exptl. Biol. Med.*, **86**, 103–7 (1954)
297. Huston, M. J., and Martin, A. W., *Arch. intern. pharmacodynamie*, **101**, 349–57 (1955)
298. Liébecq, C., *Arch. intern. physiol.*, **61**, 550–52 (1953)
299. Klebanoff, S. J., *Can. J. Biochem. Physiol.*, **33**, 780–91 (1955)
300. Umbreit, W. W., *Metabolic Maps* (Burgess Publishing Co., Minneapolis, Minn., 439 pp., 1952)
301. Albert, A., *Pharmacol. Revs.*, **4**, 136–67 (1952)
302. Friedenwald, J. S., *Pharmacol. Revs.*, **7**, 83–96 (1955)
303. Sato, T., *Acta Med. et Biol.*, (*Niigata Univ.*). **3**, 25–40 (1955)
304. Quastel, J. H., "Action of drugs on enzyme systems," pp. 523–35. In: *Enzymes: Units of Biological Structure and Function*. O. H. Gaebler, Ed., Academic Press, New York, N. Y. 624 pp., (1956)
305. Knox, W. E., Auerbach, V. H., and Lin, E. C. C., *Physiol. Revs.*, **36**, 164–254 (1956)
306. James, W. O., *Ann. Rev. Plant Physiol.*, **4**, 59–90 (1953)
307. Muir, R. M., and Hansen, C., *Ann. Rev. Plant Physiol.*, **6**, 157–76 (1955)
308. Bonner, J., and Bandurski, R. S., *Ann. Rev. Plant Physiol.*, **3**, 59–86 (1952)

RESPIRATORY SYSTEM[1,2]

By Hilding Bjurstedt

Laboratory of Aviation and Naval Medicine, Department of Physiology, Karolinska Institutet, Stockholm, Sweden

The rapid acceleration of research activities dealing with the interaction of ventilatory, circulatory, and metabolic components in the homeostasis of the body has made even an arbitrary categorization increasingly difficult. It may therefore be justified to limit this article to recent facts and theories within a few fields of investigation which either have aroused the specific interest of the reviewer or have been marked by special progress, and to appraise the present status of these fields.

Last year's review by Heemstra (98) covered much of the neurophysiology of respiration, and therefore, in this review, a greater emphasis on the chemical control of respiration may be rationalized on the grounds that this topic has of late attracted increasing interest. A comprehensive monograph by Winterstein (218) should be consulted in this connection. The problems of gas exchange in the lungs are marked by a sharpened dissociation in their treatment by physicists and clinical research workers. Special mention should therefore be made of a new publication from the Rochester group (164), which aims at presenting accumulated knowledge and new data on the complexities of gas exchange in the body in a fashion serving to bring closer the extremes. Their use of the O_2–CO_2 diagram for this purpose may safely be predicted to become a classic achievement before long. An introduction into the study of respiratory function is given by Cara (31), while clinical aspects of the respiratory system and various functional tests are reviewed by Christie & Bates (38). Rossier, Bühlmann & Wiesinger have written a comprehensive book on the physiology and pathophysiology of respiration (173), while interest was concentrated on the changes involved in pulmonary emphysema in a review by Ebert (66). Dripps & Severinghaus (62) and Whittenberger (213) have presented long-desired reviews on the influence of anesthesia on the respiratory system and of artificial respiration, respectively.

Experimental progress in the pulmonary gas exchange area goes *pari passu* with our knowledge of the pulmonary circulation, and the latter has therefore been given special consideration in the present review. Many interesting papers dealing with this subject and respiratory functions may be found in a recent symposium (163).

[1] This review covers the period from approximately May, 1955, to June, 1956. With two exceptions, the editor's request not to include abstracts has been complied with.

[2] It is a pleasure to acknowledge the secretarial work of Elisabeth Wiberg in the preparation of this review.

Chemical and Nervous Control of Ventilation

The confusion which arises from the use of many different names for comparatively simple ideas, which could well be agreed upon, is still retarding development in this field. It may be useful to substitute the term "ventilatory response" for "sensitivity of the respiratory center" to a given stimulus, when the latter may be misconstrued or does not afford any explanation as to mechanisms involved. It may be further useful to visualize the system as a closed-loop feed-back regulator, designed to minimize changes in tissue O_2, CO_2 and/or pH. As long as it is not established how the signals from peripheral and central chemoreceptors are elicited and how they affect the central integrating system under changes in, e.g., the O_2 and CO_2 tensions or in the pH, it seems futile to argue on the relative importance of any one of these quantities in the control of ventilation.

Some recent analytical reviews deal with possible characteristics of the "respiratory chemostat" as a whole (59, 60, 92, 218). Overriding controls in the form of conscious and unconscious modifications of the basic respiratory patterns and routes for their mediation are reviewed by Goldensohn (86).

Chemoreceptors.—Witzleb *et al.* (220) recorded action potentials in the carotid sinus nerve of the cat at various arterial oxygen pressures. The important observation was made that for a given change in the arterial P_{O_2} the strongest response occurred in the physiological region of 120 to 80 mm. Hg. The arterial P_{CO_2} threshold for the firing of the chemoreceptors was found to lie below 30 mm.Hg (11), but the possibility of its dependence on the buffering capacity of the blood was not analysed. It was further reported that the firing activity increased much more for a diminishing P_{O_2} than for a rising P_{CO_2} within the physiological ranges of these variables. McCubbin and associates (135) find that 5-hydroxytryptamine (serotonin), by intracarotid injection in dogs, gave rise to a much more powerful chemoreceptor discharge than, e.g., lobeline, and that intravenous doses approaching possible physiologic concentrations elicit hyperventilation only when peripheral chemoreceptor pathways are intact.

Metz (137) observed that reflex hyperventilation induced by electrical stimulation of Hering's nerve in the anesthetized dog was markedly potentiated by the introduction into the fourth ventricle of a potent anticholinesterase (tetraethyl pyrophosphate). This confirms earlier indirect evidence that a given impulse frequency in chemoceptive fibers does not necessarily reflect the integrated output of the controlling system.

Winterstein & Gökhan (219) have found a considerable increase in the ventilation after suboccipital injections of NH_4Cl, NaCN, and lobeline, and therefore suggest the existence of intracentral chemoreceptors analogous to those of the carotid and aortic bodies. Tenney & Miller (201) report a marked ventilatory stimulation after introduction of salicylate in the cisterna magna in dogs devoid of peripheral chemoreflexes.

Stretch reflexes.—The existence and possible functions of stretch receptors

of different types in the thorax have been systematically treated in a most clarifying review by Aviado & Schmidt (8). Paintal (152) located endings of vagal afferent fibers in the lungs, responding to negative intrapulmonary pressure and congestion. The receptors, which are different from the so-called deflation receptors described previously by Adrian and Paintal, were suggested to be primarily responsible for producing reflex respiratory acceleration. Green & Neil (91) demonstrated that single fibers of the recurrent laryngeal nerve of cats under chloralose showed an inspiratory discharge. This was abolished by artificial inflation of the lungs, but only with the vagi intact, which indicates pulmonary stretch receptors as the origin of the reflex inhibition. Kolder (118) observed that electrical stimulation of the vagi may lead to irreversible respiratory inhibition in rats waking up from narcosis.

Smith, Maaske & Julian (194), employing a special clamp which could be left *in situ*, noticed marked hyperpnea in intact unanesthetized dogs on constricting the main pulmonary artery, and concluded that the reflexogenic zone probably lies in the pulmonary area.

Response of alveolar ventilation to O_2 deficiency and CO_2 tension or cH or both.—Shephard (186) estimates that in normal subjects breathing 5 per cent CO_2 a steady state is reached only after 30 min., the total CO_2 accumulation during this period amounting to 1000 to 2000 ml. Cormack, Cunningham & Gee (48) report an effect, greater than additive, of the hypoxemic and CO_2 stimuli in human subjects when alveolar P_{CO_2} was kept constant at different levels by adding CO_2 as needed in the inspired gas mixture. On the other hand, Gordh & Åström (89) observed that the respiratory response to low O_2 diminished in dogs under barbiturate anesthesia when arterial cH was raised by employing the artificial ventilation and open thorax technique. Petty, Bartlett & Chapin (158) found that the "hypoxic threshold" (inspired P_{O_2} producing the first discernible increase in ventilation) was markedly elevated by ingestion of NH_4Cl and after acclimatization to 14,150 feet. Various respiratory features in acclimatization have been reviewed by Hurtado (107) and Houston (105).

Poppell *et al.* (160) find that respiratory compensation (return to normal arterial pH) is rather effective, although not complete, in experimental and clinical metabolic acidosis, whereas only a minimal respiratory compensation was observed in metabolic alkalosis (169). Singer *et al.* (189) also present data showing the tendency of arterial pH to stay elevated after infusion of sodium bicarbonate in human subjects. The two latter findings confirm earlier observations in animal experiments and supply evidence that in metabolic alkalosis the hypoxemic feed-back mechanism is protecting against a tendency of the alveolar ventilation to fall.

In situations with respiratory acidosis and CO_2 retention of long duration combined with hypoxemia, such as poliomyelitis and emphysema, the issue seems more complicated. Hypoventilation in bulbar poliomyelitis may re-

sult from damage to central chemoreceptors (124). In emphysema, Fishman, Samet & Cournand (77) find the poor ventilatory response to inhalation of CO_2 to be generally not reversible by acetazoleamide (Diamox), even though the arterial P_{CO_2} and alkali reserve may be restored toward normal levels. Judging from the ventilatory response to inspired CO_2 in air, these authors suggest that the hypoxic stimulus is rather weak. Bell *et al.* (15) report an improved alveolar ventilation after acetazoleamide, although arterial P_{CO_2} increased, which was considered evidence for inhibition of carbonic anhydrase activity of red cells. There is a marked decrease in ventilation on O_2 breathing in this disease (77, 82) which is not altered by acetazoleamide (82). In the reviewer's opinion this points to the importance of the hypoxemic component in the total ventilatory drive in a situation associated with a defective P_{CO_2} or cH feed-back mechanism, which is not easily restored.

Ruhe & Horn (174) supply evidence of differential depression of respiration by hypothermia. The hypoventilation, which according to the careful studies of Brewin *et al.* (26, 27) is concomitant with respiratory acidosis, usually with a metabolic component, may well be compatible, as is the case in general anesthesia, with a shift towards increased importance of the hypoxemic feed-back over that of P_{CO_2} or cH.

Tenney (200) presents an analytical interpretation of respiratory effects of drugs in general. The capability of salicylate to lower arterial P_{CO_2} and increase arterial O_2 saturation in emphysema with CO_2 retention is confirmed (208). The stimulating effect on ventilation seems to be exerted, at least in part, by direct action on the center, the shift in the acid-base balance being primarily one of respiratory alkalosis (201).

Exercise.—Kao *et al.* (111) observed that O_2 consumption and total ventilation increased hyperbolically to attain a steady state during electrically induced muscular exercise in decerebrate dogs, whereas a ventilatory overshoot, ascribed to cortical influence, was observed in anesthetized dogs. Voluntary exercise can be simulated by electric stimulation of large groups of trunk and thigh muscles in man (42). The concept of a neural factor generated in the exercising tissues was reinvestigated by Dejours and associates (55, 56), who find that ventilation in man falls so rapidly after cessation of light exercise that one must assume contribution of reflex influence from working muscles. Such influence was less effective when muscular movements were passively induced (56). Dejours, Mithoefer & Teillac (54) find no influence from venous chemoreceptors in man, judging from the time-lag of the respiratory response after releasing vascular occlusion of exercising legs.

Morgan and co-workers (142) showed that when deep muscular tissues of the leg in the anesthetized dog were heated selectively to temperature levels approximating those of exercise, no ventilatory changes were detectable. This suggested that pain stimuli were responsible for the results obtained during intensive heating of leg tissue.

As to humoral agents, Kao (110), by using the cross-circulation technique, showed that arterial blood from an exercising dog perfusing the head of another, was not capable of producing hyperventilation in the latter. Lambertsen (162) reports a concurrent metabolic acidosis, with partial respiratory compensation, in man during severe exercise. When high oxygen pressure (2 atm.) was applied, hyperventilation was lowered despite the fact that cerebral venous blood showed a gross elevation in P_{CO_2} and an increased cH. Oxygen therefore apparently had removed, diminished, or depressed the exercise ventilatory drive, and it appears that neither CO_2 nor cH of blood can be considered important factors in the control of ventilation in exercise. Ventilation and ventilatory equivalents for O_2 were found to be markedly increased for a given load after acclimatization to altitude without a corresponding increase in the heart rate (178).

Pulmonary Gas Exchange

Interaction of blood chemical factors and pulmonary blood flow.—Bahnson & Otis (9) have supplied an interesting review of the physiological background to surgical methods for improving blood oxygenation. In the presence of venous admixture the O_2 desaturation cannot be compensated for by hyperventilation, whereas this is theoretically the case for CO_2 admixture. The relative influence of the two chemical factors upon ventilation, as studied by creating artificial intrapulmonary shunts, is therefore of considerable interest. Dale & Rahn (51, 52), who studied the ventilatory effect of unilateral atelectasis in anesthetized dogs, observed only a partial compensation in terms of minute volume. Alveolar ventilation showed a decrease, as judged by arterial pH measurements, which was not changed significantly by blocking the perfusion of the atelectatic lung. In a thought provoking paper Born and co-workers (22) report their results from studies of the arterial O_2 saturation after obstruction of one or more bronchi, as affected by reconstruction of the ductus arteriosus in adult, anesthetized dogs. The hypothesis that the benefit of a patent ductus arteriosus in the newborn lamb is the result of recirculation of cyanosed arterial blood through the lungs could thus be tested. Opening of the ductus caused a relief of the central cyanosis, and attention was therefore drawn to the possible application of the underlying principle in widespread but nonuniform disease of the lungs.

Respiratory dead space.—Rossier & Bühlmann (172) have reviewed different methods employed in the measurement of the respiratory dead space as well as their personal concept of alveolar gas clearance. Young (222) finds, from results obtained with the infrared CO_2 analyzer, that the accepted figures for dead space during exercise must be greatly in error. Folkow & Pappenheimer (78) present the new concept of "series" (volume of respiratory passages to the alveoli) and "parallel" (alveoli which are ventilated but poorly perfused) components of the respiratory dead space,

observing that pressure breathing against 20 cm. H_2O created a parallel dead space equivalent to complete obstruction of the circulation to 10 per cent of the ventilated alveoli. Severinghaus & Stupfel (180) observed a marked increase of the anatomical dead space in man after atropine, and concluded that a significant degree of bronchomotor tone, which normally controls the volume of this space, had been removed. Histamine, epinephrine, and other broncho-active drugs gave little effect on the "series" dead space in anesthetized cats provided the transpulmonary pressure was maintained constant (78). Anatomical dead space in curarized dogs was markedly increased under artificial respiration and hypothermia, the change being ascribed to inhibition of vagal tonus under hypothermia (179). Peters (156, 157) reports a reversal of carbon dioxide-induced bronchoconstriction by atropinization or vagotomy.

Diffusion.—Bates and associates (12) describe a new steady-state CO uptake method, in which the end-tidal concentration of CO is measured directly. Forster *et al.* (80), who compared a new modification of the CO breathholding method with various other techniques, found a relatively poor agreement between the fractional uptake and the steady-state CO methods, whereas the methods for estimation of steady-state O_2 and CO diffusion provided similar values when allowance was made for the differences in physical characteristics between the two gases. Bates & Pearce (13) observed that the breathholding and steady-state (end-tidal sampling) CO methods gave closely comparable results, the diffusing capacity increasing by a mean of 3 ml. CO/min./mm.Hg when the subject lies flat. The low O_2 technique was used by Shepard and associates (183), who found a poor correlation between maximal diffusing capacity and lung volume and ventilatory capacity in chronic obstructive diseases of the airways. Gilson & Hugh-Jones (85) have supplied a comprehensive monograph on lung function in coal-worker's pneumoconiosis. These studies included simultaneous use of helium and CO to measure gas distribution and transfer, as well as a detailed and physiologically interesting interpretation.

Fink (76) finds a possibly dangerous fall in arterial O_2 saturation when nitrous oxide anesthesia is suddenly replaced by room air breathing, presumably because the outward diffusion of nitrous oxide lowers alveolar O_2 tension.

Nonuniform ventilation.—Otis and associates (150) give an interesting theoretical analysis of the influence of local differences in mechanical properties on the distribution of ventilation in the lungs, with special reference to the effects of changes in breathing frequency. Sivertson & Fowler (192), who have reinvestigated certain characteristics of CO_2 tension of expired gas, found that after several hundred ml. had been expired, the CO_2 tension of gas expired appeared to be approaching the mixed venous tension at a constant exponential rate, which characteristic is proposed for use in identifying expired alveolar gas. Luft *et al.* (127) propose the N_2 clearance

equivalent, which is independent of lung volume, as a useful lung function test. The ventilatory efficiency, as estimated by the Becklake N_2 clearance index was the same in light and moderate work as at rest (25), whereas Lundin (130) observed that eliminated N_2 is the same whether studied by N_2 percentage in end-tidal air or by N_2 washed out per breath. The single breath test has been adapted to differential bronchospirometry (49). Simmons & Hemingway (188) give data for functional residual capacity and N_2 elimination in dogs. Further studies of end-tidal N_2 concentration (90), helium uptake (69) and the use of radioactive xenon (115) as measures of ventilatory efficiency are reported.

The ventilation perfusion (V/F) ratio of the upper lobes of the dog was found to be greater than that of the lower lobes in the supine as well as the erect position (165), whereas in normal and pneumonectomized human subjects, when supine, a higher ratio has been observed in the lower lobe (132). The ventilation factor was investigated by Rahn and associates (165), who found in dogs, by using a radioactive aerosol inhalation technique, a lesser ventilatory activity per unit lung in the lower lobes in the supine, and a reversed situation in the erect position. Bronchospirometric studies in human subjects in lateral decubitus positions led to the conclusion that the dependent lung usually increases its relative ventilation (139).

Alveolar-arterial gas differences.—The three independent factors responsible for the alveolar-arterial O_2 difference, namely, diffusion, venous admixture, and unequal V/F ratios among the alveoli, have been excellently treated in a theoretical analysis by Fahri & Rahn (74), with special regard to the distribution effect when the lung is exposed to various inspired O_2 tensions. Perkins *et al.* (155) describe a method for the semiquantitative evaluation of these factors, using the oximeter and alveolar P_{O_2} determinations. Bartels *et al.* (10) found in human subjects breathing 50 per cent O_2 that the calculated venous admixture was 1 per cent at rest and 0.87 per cent in exercise, and concluded that during exercise the time spent by the blood in the pulmonary capillaries is sufficient also during air breathing for O_2 equilibration in the lungs. With a modified Riley technique, Atwell *et al.* (7) found no oxygen loss across the membrane lining of the left ventricle or on the way to peripheral arteries. The alveolar-arterial P_{O_2} difference in dogs, as affected by opening the chest, was studied by Williams (214).

Pulmonary Circulation

Pressures and flow.—Pressure measurements in the left atrium have been made by Allison (163), with a needle inserted down a bronchoscope, with the aim of differentiating between cases of mitral stenosis and mitral insufficiency. Björk & Malmström (19) employed the technique of right-sided paravertebral puncture of the left atrium for studies of pressure curves during increased intrapulmonary pressure, observing that the right and left atrial pressures increased by the same amount in a normal subject,

whereas cases of mitral stenosis showed a greater increase in the right atrium. The hemodynamic implications are difficult to judge, since intrathoracic or net vascular pressures were not measured (admittedly an unreasonable demand in a procedure of this kind, whether the subject is normal or not). Acutely increased resistance in the systemic arterial tree may be compatible with relatively low vascular pressures and blood volume in the lungs because of the restraining influence of the pericardium on the right ventricular stroke work, as the left ventricle is differentially stressed and dilated (16).

Henry *et al.* (100), who measured left and right atrial pressures in anesthetized dogs, suggest that, for small blood volume changes, the atria, being the most distensible parts of the low pressure system, would seem to be the perfect place for stretch receptors involved in a mechanism for the regulation of the blood volume, which was previously postulated (99).

Interest continues in wedged-catheter pressures. Several authors have already dropped the quotation marks around "pulmonary capillary pressure," although at present no method of measuring true pulmonary capillary pressure is available. The impacted small vein pressure has been compared with the pulmonary artery pressure pulse (83). Where comparison was possible the pressure levels and contours were similar in the same patients, indicating that the pulmonary flow and resistance had little effect on the transmission of the pulmonary artery pressure across the capillary bed.

The determination of cardiac output has a methodological interest, especially in exercise and oxygen deficiency, as one of the necessary parameters in measurements of pulmonary vascular resistance. Asmussen & Nielsen (5) adopted the conventional dye-injection method for measurement of cardiac output in man at rest and during work under low O_2 breathing, observing an increase of 10 to 20 per cent above values from control experiments with air breathing. Rapaport *et al.* (167) found in anesthetized dogs breathing air a good agreement between cardiac outputs determined by means of the conventional dye-dilution method (plasma) and the radioactive Cr^{51} method (red cell). A modification of the recently introduced constant-rate dye-injection method was proposed for use in man, the dye being injected into the right ventricle or pulmonary artery (187).

Lee & DuBois (123), by using Krogh's nitrous oxide technique with the subject sitting in a body plethysmograph, have been able to calculate instantaneous pulmonary capillary blood flow events by reading the pressure fluctuations in the plethysmograph, demonstrating in this rather ingenious way that the capillary blood flow is highly pulsatile (peak blood flow at rest about 12.5 l./min., slowest flow about 3 l./min.), the pulsatility having a tendency to increase with exercise. These findings bring up the question of critical closing pressures for the smaller lung vessels, and whether critical closing may be prevented by stagnation with a sufficiently high transcapillary pressure.

Rodbard (170) studied some rheological aspects of the pulmonary circulation by means of a model manifold of glass and rubber tubes, outlining implications of effects of various conditions on flow and pressures. Bronchospirometrical studies of the relative perfusion of the upper lobe and the basal lobes of the right lung in man demonstrated a decreasing perfusion of the upper lobe as the position of the subject was changed from the supine to the erect (134), whereas a comparison between the two lungs in the lateral decubitus position showed an increased flow in the dependent lung (139).

The subject of changes in pulmonary vascular resistance (PVR) and flow in relation to changes in the intrathoracic pressure was reviewed by Whittenberger (213). The old question of whether during inspiration the increased inflow is concomitant with increased or decreased PVR has created a new facet in the tackling of another problem, that of the origin of the decreased flow during positive pressure inflation. Thus Hubay, Brecher & Clement were able to demonstrate, again with the bristle flow meter (106), that during inflation of the lungs by mild positive pressure in open-chest experiments on dogs, increased PVR is a factor contributing to the reduction of flow. Reducing the lumen of the main pulmonary artery in intact unanesthetized dogs by 65 to 70 per cent caused the systemic mean blood pressure to level off at about 30 to 40 mm. Hg with a considerable rise of central venous pressure, but with a secondary hemodynamic equilibrium being reestablished if restriction were continued (194).

Response to hypoxia.—The site of action of hypoxia in the pulmonary circuit (arteriolar vs. venular effects) and the mechanism involved in the response are under lively discussion, but these problems are still largely unsolved. Blakemore *et al.* (20), contrary to recent findings by other investigators, report a redistribution of the pulmonary blood flow from the hypoxic lung during unilateral rebreathing in man, while in the lateral decubitus position blood flow increased in the dependent lung whether rebreathing low or high O_2. In animals, after temporary fall in cardiac output, a secondary increase in the systemic arterial and mixed venous O_2 saturation was observed, which was interpreted as being due to a redistribution of blood from the rebreathing lung and an increase in cardiac output (206).

Extrinsic control of vasomotion, reflex mechanisms and drugs.—Recent work on pulmonary vasomotor nerve activity and its possible functional significance has been reviewed by Daly (163). That vasoconstriction may easily be demonstrated in animal experiments is well established, but the main pathways and the destination of responsible vasomotor fibers are uncertain. As to the extrinsic control of vasomotion in human lungs opinions differ, one group of workers taking a nihilistic view, others being more positive. The adrenergic nerve supply to the lung is small, even though this organ is rich in vessels. Accordingly, the norepinephrine content of lung tissue is quite low (72). The results obtained in animals may represent a

physiological potentiality of the lungs rather than a normal working mechanism. Donald (163) suggests that the vasomotor capabilities of the pulmonary vessels may be an example of a vestigial function which is no longer of importance in the healthy individual. Occlusion of the common carotid arteries caused a reflex rise in pulmonary arterial pressure in anesthetized dogs, while stimulation of the sinus nerve produced a fall, both effects being at least in part secondary to extrapulmonary cardiovascular changes (53).

Niden & Aviado (148) report the presence of powerful intrapulmonary reflexes, partly carried by the extrinsic pulmonary nerves, on injection of glass beads in dogs under chloralose and morphine, whereas Williams (215), using dogs under sodium barbital, found no evidence for reflex spasm, judging from the absence of an influence of hexamethonium or denervation on the behaviour of the pulmonary arterial pressure. Price, Hata & Smith (161) observed that, in heart-lung-head preparations, embolization with small quantities of barium sulphate suspension caused vastly increased PVR, which could be prevented by hexamethonium and by previous sympathetic denervation.

During infusion through the pulmonary artery in the dog norepinephrine as well as epinephrine caused a rapid transient rise of pulmonary arterial pressure and a fall in pulmonary venous pressure (73). These agents have also been studied with the left ventricle replaced by a mechanical pump for exclusion of drug actions on the heart and systemic blood vessels, a method which appears to be useful also for studying effects of other humoral agents on vasomotion in the lungs (171). After single injections in the pulmonary artery, a direct vasoconstrictor effect with a rise in pulmonary arterial pressure and a decrease in pulmonary venous flow was observed, the pulmonary artery pressure response becoming greater when the drugs entered the systemic circulation.

Intrathoracic blood volume.—The reservoir function of the lung vessels has been reviewed by Sjöstrand (193), who makes a most timely proposal that "hemodynamic reserve blood" be substituted for "depot," the former expression being taken to stress the fact that the pulmonary blood volume is at no time excluded from the total active circulation. Asmussen & Nielsen (6) doubt that changes in the blood content of the thorax can be determined quantitatively from changes in the mean capacity of the lungs, as previously claimed by Sjöstrand, and therefore challenge the latter's recent experimental findings concerning the shift of blood from the lower extremities to the thorax in man on assuming the recumbent position. So far no conclusive data have been presented on the possible role of the pulmonary circulation as an actively regulated blood reservoir, although intravenous infusion of norepinephrine has been reported to shift blood to the heart and lungs in anesthetized dogs (181). Etsten & Li (71) observed a reduction of the intrathoracic blood volume by around 25 per cent during deep surgical anesthesia.

Sharpey-Schafer (182) used the Valsalva maneuver as an interesting

and simple method for studying differences between the normal and failing circulation, whereas its use as a test for pulmonary congestion was described by Knowles, Gorlin & Storey (116).

Kattus and co-workers (112), by studying curves obtained from single injection of dye, found that the "central blood volume," believed to be closely related to pulmonary blood volume, averaged 0.590 l. in normal subjects. Some doubt has recently been cast on the theoretical basis of the slope-output method by Hetzel, Swan & Wood (101), who observed increasing central and pulmonary blood volumes as the site of the injection of the dye was moved from the pulmonary artery peripherally towards the antecubital vein. The arteriovenous equilibration method using Cr^{51} or dye resulted in pulmonary blood volumes lower than those obtained by the mean circulation time-output method (167). The technique of calculating the pulmonary blood volume by determining the total blood volume between the pulmonary artery and the brachial artery with the dye-dilution method and subtracting the x-ray volume of the heart and part of the arterial system has been further developed by Comét & Lagerlöf (45, 46).

Arterial-venous shunts, collateral circulation.—Stork (198), in a review of pulmonary arteriovenous fistulas, describes various techniques in the diagnosis of such lesions. Steinberg & McClenahan (196) describe angiocardiographic observations of pulmonary arteriovenous fistulas and changes in size of the lesions under negative and positive intrapulmonary pressure. Bostroem & Piiper (24) concluded from experiments on isolated lobes of dog lungs, with injection of beads combined with determination of the venous admixture, that beads with a diameter of 19 μ must have passed through capillaries engaged in the gas exchange.

The magnitude and time factor of development of collateral circulation to the left lung in dogs after occlusion of the left pulmonary artery was investigated by Williams & Towbin (216), who found that after one year there was an increase in the collateral flow up to between 68 and 376 cc./min. from an original 4.4 to 9 cc./min.

Abnormal Barometric Pressures

High oxygen pressure.—Massion (133) has reviewed different deleterious actions of high oxygen pressures. The debate on the nature of oxygen toxicity has been reactivated in the cruising between the Scylla of oxygen toxicity and the Charybdis of bends in self-contained diving with nitrogen-oxygen mixtures. The nature of the neural insult delivered by high arterial oxygen pressure has been extensively treated in a recent underwater physiology symposium (162). Lambertsen *et al.* have continued their studies on the effect of high oxygen pressures on the arterial and internal jugular blood gas composition in man, finding that addition of 2 per cent CO_2 to O_2 inhaled at 3.5 atm. pressure caused an average increase of internal jugular venous P_{O_2} of nearly 1000 mm.Hg above the level found during breathing O_2 alone.

They propose that the latent period of O_2 toxicity is shortened by CO_2 inhalation via cerebral vasodilatation, which increases the dose of the toxic agent in the brain or the number of cells exposed (120). Recent investigations made by this group have been analyzed by Winterstein (218), who points out that the original idea of Gesell that the hyperpnea of high oxygen pressure may be caused by intracentral CO_2 retention has not been contested, even if such a mechanism cannot account for poisonous effects of high oxygen pressures. Chapin (35) observed that mice, convulsing on pure oxygen, went on to die without convulsion, if CO_2 were added at partial pressures exceeding 120 mm.Hg, or about 16 per cent of 1 atm. This anticonvulsant threshold of CO_2 appears to be of special significance, since mice receiving less CO_2 convulsed sooner than those receiving pure O_2.

Some additional evidence that oxidation of SH-coenzymes is involved in the toxic action of high oxygen pressures is presented by Haugaard (162), in support of the concept that inactivation of tissue enzymes causes toxic symptoms under high oxygen pressures. Taylor (199), in experiments on rats, found that lung damage was connected with the absence or presence of α-tocopherol, while methylene blue was effective only in delaying the disturbances in the nervous system. In this connection, hormonal causative factors are discussed by Bean (162), while Schaefer (177), judging by the pulse rate changes in underwater swimming during O_2 breathing, suggests a transition from strong parasympathetic activity to increased sympathetic tone as toxic symptoms develop. The latter author, who advocates the use of nonresponsiveness or fixation of pulse rate as a warning for acute symtoms of O_2 toxicity, also observed rapid, shallow breathing and inspiratory inhibition, which likewise lead him to assume an activation of the vagal inhibitory reflex mechanism; this might possibly also be responsible for the well known reduction of exercise hyperpnea under high oxygen pressures. Stein & Perot (195) have shown that the action potential of peripheral nerve is depressed by high oxygen pressure and that mammalian nerve is more vulnerable than amphibian. Stein has also reviewed various neurophysiological effects of high oxygen pressures (162), stressing the need for a better comprehension regarding the relationships between the hyperoxic convulsion and the mechanisms of epilepsy and other convulsive phenomena.

Lanphier (121) presents various problems encountered in the use of nitrogen-oxygen mixtures in diving, whereas Webster (162) discusses some theoretical aspects of the use of multiple-gas mixtures for deepsea diving.

The fact that oxygen may enhance tissue damage caused by irradiation, this possibly having a connection with the recent suggestion that oxygen poisoning and the effects of irradiation have a mechanism in common, has stimulated the use of simultaneous O_2 respiration at 3 atm. and x-ray treatment of patients, with carcinomata, yielding strikingly good results (39, 175). Evidence that irradiation of mice may increase their sensitivity to high oxygen pressures initially but provide a striking protection after longer

periods of time has been presented by Gilbert, Gerschman & Fenn, who find that the latter effect can be attributed to irradiation anorexia (84).

Decompression sickness.—Behnke (14) and Vavala (205) have reviewed various aspects of decompression sickness, while the former author also outlines several unsolved problems of decompression and bends as well as of high oxygen pressure (162). Harvey discusses the physics of bubble formation in the tissues (162). An extensive study of pathological lesions resulting from decompression sickness in airmen, caisson workers, and divers has been published by Haymaker & Johnston (96). Donald (57), who exposed goats to 64 per cent O_2 and 36 per cent N_2 for 1 hr. at 5.54 atm., observed symptoms of grave decompression sickness upon returning to air breathing at atmospheric pressure with rapid remission of symptoms when recompression was omitted. This and other evidence introduce the concept of "oxygen bends" as a factor in certain types of decompression sickness. The role of a patent foramen ovale in severe and fatal cases of decompression sickness has been pointed out by Haymaker, Johnston & Downey (97).

Explosive decompression.—Collected papers on aviation medicine (43) include considerations of the physiological consequences of loss of cabin pressure in high-altitude aircraft (Fryer) and of physiological requirements of pressure cabins (Roxburgh). The sequelae of rapid and explosive decompression have been reviewed by Kolder (117), who suggests that the latter term should be reserved for decompression fast enough to cause injuries similar to "blast effects." In experiments on rats subjected to "explosive positive pressure decompression," results were obtained which were taken to indicate that the mortality rate is determined by the decompression time and not by the pressure change. Whether the absolute pressure factor can be left out of consideration seems dubious, since the absolute pressure change must provide the energy for the production of lesions, whether the decompression is explosive or less rapid. Violette (207) reports that the thoracic cage remains immobile during somewhat less than 10 msec. immediately after explosive decompression, as judged by the aid of ultrarapid cinematography and transthoracic pressure recordings. Transthoracic pressure changes in man resulting from explosive decompression under well controlled conditions have also been described by Luft & Bancroft, together with a theoretical treatment of the physical factors involved (125). Their results indicate that the danger of lung injury increases with the transthoracic pressure buildup and that attempts to define safe conditions for decompression should be based on knowledge of airway resistance under the dynamic circumstances of rapid decompression.

Differences in the etiology of lung injury from explosive decompression and blast are discussed by Clemedson (40), who found no correlation between the respiratory phase and the extent of lung injury in rabbits exposed to high explosive shock waves, whereas in mice the injurious effect increased with the duration of the shock wave judged from the mortality rate (33).

Pressure recordings were also made by means of a high frequency barium-titanate pressure transducer introduced in the right pleural sac in rabbits exposed to high explosive shock waves (41).

A series of bold experiments by Luft & Noell (126), in which two subjects under O_2 breathing were exposed to pressures of 68 to 70 mm. Hg, starting at an original level of 200 mm. Hg, yielded extremely interesting results. Symptoms of rapid cerebral impairment were described, the electroencephalogram showing abnormally slow frequencies and temporary absence of brain activity. These experiments also showed that the net anoxic survival time of the most sensitive of the major integrating systems of cerebral activities appears to be 4 to 5 secs. and that loss of comprehension (unconsciousness) occurs after 7 to 8 secs.

Miscellaneous.—Other papers of importance in connection with the respiratory system, presented in the aforementioned symposium on underwater physiology (162), included physiological aspects of breathholding at increased atmospheric pressure (DuBois), changes in resistance to breathing at increased ambient pressure (Mead), the role of CO_2 in the physiology of human diving (Schaefer), and a discussion of factors determining the isonarcotic pressures of various so-called inert gases (Carpenter). The problem of nitrogen narcosis has also been reviewed by Burnett (28).

Artificial Respiration and Allied Topics

It is not within the scope of a review of this type to give an account of the many new devices for artificial respiration. Physiological aspects of the function of the respiratory system in artificial ventilation have been exellently reviewed by Whittenberger (213), who stresses the all-important necessity of providing optimal conditions for the cardiovascular component, and by Donald & Paton (58). It seems at present most urgent to encourage investigation into the circulatory response to different procedures, especially in situations requiring prolonged therapy, such as poliomyelitis and emphysema, and in those aggravated by a failing circulation.

As might be expected, intermittent positive pressure ventilation reduces cardiac output in spontaneously breathing poliomyelitis patients (17). The authors believe that a decrease in the blood reserve in the lungs might contribute to the decrease in cardiac output. Tilting to 6° to 10° head-low position during intermittent positive pressure ventilation produced an increase of cardiac output and stroke volume in poliomyelitis patients with respiratory paralysis, while in anesthetized surgical patients under meperidine (Pethidine) and succinylcholine only the stroke volume increased (18).

The effects of positive pressure ventilation on the circulation has been studied in more detail in high pressure breathing, employed by aviators for protection from exposure to very low atmospheric pressure. With suitable counterpressure over the body, intrapulmonic pressures as high as 150 mm. Hg or more (breathing O_2) are used, which should secure sufficient arteriali-

zation even at near vacuum. Employing the inflated pressure waistcoat covering the entire trunk (the jerkin) for counterpressure, Ernsting (70) found a linear relationship between the volume of blood pooled in a limb and the breathing pressure, the distensibility of the vasculature of the upper extremity amounting to two and one half times that of the lower. Filtration of fluid from capillaries in the unprotected limb also increased linearly with the breathing pressure up to around 100 mm. Hg, amounting to approximately 0.005 ml. fluid/100 ml. limb/min. in the upper limb and considerably less in the lower. A reduction of the effective circulating blood volume by about 750 ml. was found during pressure breathing at 50 mm. Hg for 11 min., and at 135 mm. Hg for 1 min. Vaso-vagal attacks were observed when the blood volume reduction exceeded 650 to 900 ml. Blood flow to the extremities was studied by Shephard (184), using needle thermocouples inserted in the brachio-radialis muscle. An initial temperature peak during pressure breathing was taken to indicate an increase of flow, whereas after a while rapid cooling ensued. The latter was ascribed to a secondary peripheral vasoconstriction.

Diffusion respiration, perhaps more correctly describable as apneic oxygenation (144) (since diffusion is always present where there is gas exchange), has drawn continued attention. The increase in arterial and tissue cH and P_{CO_2} and changes in O_2 uptake, as well as arterial O_2 saturation, were studied by Holmdahl (104), largely by use of a technique of continuously measuring the arterial pH and oxygen saturation earlier developed in this laboratory. In anesthetized dogs under succinylcholine a progressive metabolic acidosis occurred in addition to the expected respiratory acidosis. In patients, an average increase of the arterial P_{CO_2} of about 30 mm. Hg was observed at the end of a six min. period of apnea, during which the calculated arterial pH decreased by about 0.16 units. Cardiac output increased at the end of the apneic period, as estimated from the product of heart rate and pulse pressure. In the dogs a fall was noted instead when the cardiac output was measured by the Fick method, while an increase was observed by Nahas & L'Allemand (144) in similar experiments on dogs under d-tubocurarine and pentobarbital, using the dye-dilution method. Differences in the results of these two investigations might possibly be explained by the higher dosage of pentobarbital used by Holmdahl, since there is evidence that this drug exerts a specific action on the myocardium and cardiovascular system (145).

General

Mechanics and work of breathing.—A review of the mechanics of ventilation is given by Cara (32). DuBois and associates describe their rapid methods using a body plethysmograph, and give data for thoracic gas volume (64) and airway resistance (65) in human subjects. Physical properties of the lungs have been studied in emphysema (36, 136) and in diffuse pulmonary fibrosis (2). The hindrance component of cat lungs was studied by

Mount (143). Effects of changes in the pulmonary blood pressure on the elastic resistance of the lungs were described by Jiménez-Vargas (108). Abdominal muscle activity in respiration was discussed by Campbell (30).

Butler & Arnott (29) supply evidence that the increased work of ventilation in normal subjects in the expiratory position is mainly due to increased viscosity, and to an increased elastic component in the inspiratory position. In anesthetized cats O_2 consumption depends more on the integrated muscle activity, as measured by an electromyogram technique, than on either total ventilation or respiratory frequency (166). Margaria & Marro (131) propose the use of maximum potential work of breathing as a functional respiratory test.

Pulmonary edema.—Luisada (128) has presented a survey of the physiopathology and clinical management of pulmonary edema. The influence of pulmonary lymph circulation (81) and of the alveolar lining layer were discussed (153, 159). Further reports on the beneficial actions of silicone aerosols (129, 147), and alcohol vapor (129, 210) are available.

Fetal and neonatal respiration.—Various factors determining the viability of premature lambs are discussed (21). The specific sensitivity of the ductus arteriosus to changes in O_2 tension has been studied (23). The ductus may cause a veno-arterial shunt of considerable magnitude, persisting in a significant number of newborn infants up to 72 hours of life (68). The comparatively rapid respiration in the newborn infants is probably optimal because of elastic and viscous properties of the lung (47). The effects of acute hypoxia suggest that chemoreflex influence is less active immediately following birth than later on in life (138). Methods suitable for respiratory studies in newborn infants have been described (63, 197).

Miscellaneous.—Whalen (211) studied respiratory patterns in anesthetized cats after hyperventilation; these were thought to support the hypothesis of one chemosensitive and one reflex respiratory center. The breath-holding breaking point was associated with a decreased alveolar P_{O_2} and increased P_{CO_2} when the technique of rebreathing exhaled air every 20 sec. was employed (221), whereas breathholding with various lung volumes was reported not to influence the "breathholding curve," as expressed by the O_2-CO_2 diagram (34).

Techniques.—Methods for study of the following have been described: O_2 tension in blood (61, 140, 204, 217), in tissues (113, 176), and in other biological fluids (67); O_2 saturation in blood (1, 93, 94, 103, 141, 203); O_2 content and saturation in hemoglobin dissociation curve determinations (151); CO in air (3, 114) and in blood (4, 37, 122, 146); respiratory gases by means of quantitative emission spectroscopy (212); alveolar CO_2 (43, 44) and single-breath CO_2 (75); CO_2 tension of the mixed venous blood entering the lungs by a CO_2 equilibration procedure (79); pH and CO_2 content of blood (190); CO_2 content of serum (109) and plasma (102); CO_2 and O_2 contents of whole blood (102). Arterial and cutaneous "arterialized" blood are virtually

identical in acid-base properties (190) and in O_2 content (209). Properties and use of the nitrogen meter are described (43, 185), and gas volume correction tables for cardiopulmonary laboratories have been prepared (119).

A simple apparatus for measurement of respiratory pressure-volume relationships (149) and a new type of flow resistor for respiratory studies (87), as well as a device for filling spirometers automatically (202), a tracheal cannula for experimental separation of dog lungs (50), an apparatus for chronic exposure of rats to low P_{O_2} (191) and methods for blood oxygenation in animal experiments (88, 95, 154, 168) have been described.

LITERATURE CITED

1. Albers, C., and Brendel, W., *Pflügers Arch. ges. Physiol.*, **260**, 345-57 (1955)
2. Alexander, J. K., *J. Lab. Clin. Med.*, **46**, 791–92 (1955)
3. Allen, T. H., and Root, W. S., *J. Biol. Chem.*, **216**, 309–17 (1955)
4. Allen, T. H., and Root, W. S., *J. Biol. Chem.*, **216**, 319–23 (1955)
5. Asmussen, E., and Nielsen, M., *Acta Physiol. Scand.*, **35**, 73–83 (1955)
6. Asmussen, E., and Nielsen, M., *Physiol. Revs.*, **35**, 778–800 (1955)
7. Atwell, R. J., Ryan, J. M., Hull, H. B., and Tomashefski, J. F., *Am. J. Physiol.*, **183**, 451–53 (1955)
8. Aviado, D. M., Jr., and Schmidt, C. F., *Physiol. Revs.*, **35**, 247–300 (1955)
9. Bahnson, H. T., and Otis, A. B., *Physiol. Revs.*, **35**, 363–80 (1955)
10. Bartels, H., Koepchen, H. -P., Lühning, I., Mochizuki, M., and Witt, I., *Pflügers Arch. ges. Physiol.*, **261**, 535–42 (1955)
11. Bartels, H., and Witzleb, E., *Pflügers Arch. ges. Physiol.*, **262**, 466–72 (1956)
12. Bates, D. V., Boucot, N. G., and Dormer, A. E., *J. Physiol. (London)*, **129**, 237–52 (1955)
13. Bates, D. V., and Pearce, J. F., *J. Physiol. (London)*, **132**, 232–38 (1956)
14. Behnke, A. R., *Military Med.*, **117**, 257–71 (1955)
15. Bell, A. L. L., Jr., Smith, C. N., and Andreae, E., *Am. J. Med.*, **18**, 536–46 (1955)
16. Berglund, E., Sarnoff, S. J., and Isaacs, J. P., *Circulation Research*, **3**, 133–39 (1955)
17. Bernéus, B., and Carlsten, A., *Acta Med. Scand.*, **152**, 19–30 (1955)
18. Bernéus, B., Gordh, T., Linderholm, H., Ström, G., and Werneman, H., *Acta Med. Scand.*, **152**, 31–38 (1955)
19. Björk, V. O., and Malmström, G., *Am. Heart J.*, **50**, 742–48 (1955)
20. Blakemore, W. S., Carlens, E., and Björkman, S., *Surg. Forum: Clin. Congr. Am. Coll. Surgeons*, **5**, 691–96 (1954) (1955)
21. Born, G. V. R., Dawes, G. S., and Mott, J. C., *J. Physiol. (London)*, **130**, 191–212 (1955)
22. Born, G. V. R., Dawes, G. S., Mott, J. C., and Rennick, B. R., *J. Physiol. (London)*, **130**, 167–90 (1955)
23. Born, G. V. R., Dawes, G. S., Mott, J. C., and Rennick, B. R., *J. Physiol. (London)*, **132**, 304–42 (1956)
24. Bostroem, B., and Piiper, J., *Pflügers Arch. ges. Physiol.*, **261**, 165–71 (1955)
25. Bouhuys, A., Hagstam, K. -E., and Lundin, G., *Acta Physiol. Scand.*, **35**, 289–304 (1956)
26. Brewin, E. G., Gould, R. P., Nashat, F. S., and Neil, E., *Guy's Hosp. Rep'ts.*, **104**, 177–214 (1955)
27. Brewin, E. G., Nashat, F. S., and Neil, E., *Brit. J. Anaesthesia*, **28**, 2–12 (1956)
28. Burnett, W. A., *J. Roy. Naval Med. Service*, **41**, 188–92 (1955)
29. Butler, J., and Arnott, W. M., *Clin. Sci.*, **14**, 703–10 (1955)
30. Campbell, E. J., *Arch. Middlesex Hosp.*, **5**, 87–94 (1955)
31. Cara, M., *Poumon et le coeur*, **11**, 819–35 (1955)
32. Cara, M., *Poumon et le coeur*, **11**, 969–95 (1955)
33. Celander, H., Clemedson, C. -J., Ericsson, U. A., and Hultman, H. I., *Acta Physiol. Scand.*, **33**, 14–18 (1955)
34. Chapin, J. L., *J. Appl. Physiol.*, **8**, 88–90 (1955)
35. Chapin, J. L., *Proc. Soc. Exptl. Biol. Med.*, **90**, 663–64 (1955)

36. Cherniach, R. M., *J. Clin. Invest.*, **35**, 394–404 (1956)
37. Chinn, H. I., Pawel, N. E., and Redmond, R. F., *J. Lab. Clin. Med.*, **46**, 905–9 (1955)
38. Christie, R. V., and Bates, D. V., *Ann. Rev. Med.*, **6**, 211–24 (1955)
39. Churchill-Davidson, I., Sanger, C., and Thomlinson, R. H., *Lancet*, **268**, 1091–95 (1955)
40. Clemedson, C. -J., *J. Appl. Physiol.*, **7**, 38–42 (1954)
41. Clemedson, C. -J., and Pettersson, H., *Am. J. Physiol.*, **184**, 119–26 (1956)
42. Cogswell, R. C., Jr., and Browner, W. J., *J. Appl. Physiol.*, **8**, 19–21 (1955)
43. *Collected Papers on Aviation Medicine, AGARDograph No. 6* (Butterworths Scientific Publications, London, England, 209 pp., 1955)
44. Collier, C. R., Affeldt, J. E., and Farr, A. F., *J. Lab. Clin. Med.*, **45**, 526–39 (1955)
45. Comét, S., and Lagerlöf, H. O., *Acta Physiol. Scand.*, **36**, 337–47 (1956)
46. Comét, S., and Lagerlöf, H. O., *Acta Physiol. Scand.*, **36**, 348–59 (1956)
47. Cook, C. D., Cherry, R. B., O'Brien, D., Karlberg, P., and Smith, C. A., *J. Clin. Invest.*, **34**, 975–82 (1955)
48. Cormack, R. S., Cunningham, D. J. C., and Gee, J. B., *J. Physiol. (London)*, **129**, 29–30P (1955)
49. Curtis, J. K., Cree, E., Rasmussen, H., and Mendenhall, J. T., *J. Thoracic Surg.*, **30**, 702–12 (1955)
50. Dale, W. A., and Rahn, H., *J. Thoracic Surg.*, **29**, 453–57 (1955)
51. Dale, W. A., and Rahn, H., *J. Thoracic Surg.*, **29**, 458–66 (1955)
52. Dale, W. A., and Rahn, H., *Surg. Forum: Clin. Congr. Am. Coll. Surgeons*, **5**, 697–702 (1954–1955)
53. Daly, M. deB., and Schweitzer, A., *J. Physiol. (London)*, **131**, 220–42 (1956)
54. Dejours, P., Mithoefer, J. C., and Teillac, A., *J. Physiol. (Paris)*, **47**, 160–63 (1955)
55. Dejours, P., Raynaud, J., Cuénod, C. L., and Labrousse, Y., *J. Physiol. (Paris)*, **47**, 155–59 (1955)
56. Dejours, P., Teillac, A., Labrousse, Y., and Raynaud, J., *Revue Française d'Etudes Cliniques et Biologiques*, **1**, 504–17 (1956)
57. Donald, K. W., *J. Appl. Physiol.*, **7**, 639–44 (1955)
58. Donald, K. W., and Paton, W. D., *Brit. Med. J.*, **1**, 313–17 (1955)
59. Dornhorst, A. C., *Lancet*, **I**, 1185–87 (1955)
60. Dornhorst, A. C., *St. Thomas's Repts.*, **8**, 69–86 (1952)
61. Drenckhahn, F. -O., *Pflügers Arch. ges. Physiol.*, **262**, 169–80 (1956)
62. Dripps, R. D., and Severinghaus, J. W., *Physiol. Revs.*, **35**, 741–77 (1955)
63. Drorbaugh, J. E., and Fenn, W. O., *Pediatrics*, **16**, 81–87 (1955)
64. DuBois, A. B., Botelho, S. Y., Bedell, G. N., Marshall, R., and Comroe, J. H., Jr., *J. Clin. Invest.*, **35**, 322–26 (1956)
65. DuBois, A. B., Botelho, S. Y., and Comroe, J. H., Jr., *J. Clin. Invest.*, **35**, 327–35 (1956)
66. Ebert, R. V., *Ann. Rev. Med.*, **7**, 123–40 (1956)
67. Eggers, L. H., *Scand. J. Clin. Lab. Invest.*, **7**, 181–87 (1955)
68. Eldridge, F. L., and Hultgren, H. N., *J. Clin. Invest.*, **34**, 987–96 (1955)
69. Englert, M., Denolin, H., and De Coster, A., *J. français méd. chir. thorac.*, **9**, 14–35 (1955)
70. Ernsting, J., *Flying Personnel Research Committee (Great Britain), Rept. No. 926* (RAF Institute of Aviation Medicine, 23, 1955)

71. Etsten, B., and Li, T. H., *J. Clin. Invest.*, **34,** 500–10 (1955)
72. von Euler, U. S., *Noradrenaline* (Charles C Thomas, Publisher, Springfield, Illinois, 382 pp., 1955)
73. Ewing, P. L., Atkinson, G., and Seager, L. D., *J. Pharmacol. Exptl. Therap.*, **113,** 19–20 (1955)
74. Fahri, L. E., and Rahn, A., *J. Appl. Physiol.*, **7,** 699–703 (1955)
75. Feinmann, L., Leathart, G. L., and Pendlenton, G. B., *Nature*, **176,** 739–40 (1955)
76. Fink, B. R., *Anesthesiology*, **16,** 511–19 (1955)
77. Fishman, A. P., Samet, P., and Cournand, A., *Am. J. Med.*, **19,** 533–48 (1955)
78. Folkow, B., and Papperheimer, J. R., *J. Appl. Physiol.*, **8,** 102–10 (1955)
79. Forssander, C. A., *J. Appl. Physiol.*, **8,** 509–12 (1956)
80. Forster, R. E., Cohn, J. E., Briscoe, W. A., Blakemore, W. S., and Riley, R. L., *J. Clin. Invest.*, **34,** 1417–26 (1955)
81. Földi, M., Kepes, J., Rusznyák, I., and Szabó, G., *Acta Med. Acad. Sci. Hung.*, **7,** 345–69 (1955)
82. Galdston, M., *Am. J. Med.*, **19,** 516–32 (1955)
83. Gensini, G., Balchum, O. J., and Blount, S. G., Jr., *Am. Heart J.*, **49,** 507–16 (1955)
84. Gilbert, D. L., Gerschman, R., and Fenn, W. O., *Am. J. Physiol.*, **181,** 272–74 (1955)
85. Gilson, J. C., and Hugh-Jones, P., *Lung Function in Coalworker's Pneumoconiosis* (Medical Research Council, Special Report Series, No. 290, London, England, 266 pp., 1955)
86. Goldensohn, E. S., *Psychosomat. Med.*, **17,** 377–82 (1955)
87. Goldsmith, J. R., and Young, A. C., *J. Appl. Physiol.*, **8,** 562–64 (1956)
88. Gollan, F., *J. Appl. Physiol.*, **8,** 571–72 (1956)
89. Gordh, T., and Aström, A., *Anesthesiology*, **16,** 245–53 (1955)
90. Gray, F. D., Jr., Gray, F. C., and Dillinger, G. E., Jr., *J. Chronic Diseases*, **2,** 146–55 (1955)
91. Green, J. H., and Neil, E., *J. Physiol. (London)*, **129,** 134–41 (1955)
92. Grodins, F. S., Gray, J. S., Schroeder, K. R., Norins, A. L., and Jones, R. W., *J. Appl. Physiol.*, **7,** 283–308 (1954)
93. Handforth, C. P., *Lancet*, **268,** 1252–53 (1955)
94. Hartleb, O., *Deut. Gesundheitsw.*, **10,** 1001–4 (1955)
95. Hayes, E. W., Jr., Morse, D. P., Jamison, W. L., and Bailey, C. P., *Proc. Soc. Exptl. Biol. Med.*, **89,** 413–15 (1955)
96. Haymaker, W., and Johnston, A. D., *Military Med.*, **117,** 285–306 (1955)
97. Haymaker, W., Johnston, A. D., and Downey, V. M., *J. Aviation Med.*, **27,** 2–17 (1956)
98. Heemstra, H., *Ann. Rev. Physiol.*, **17,** 121–44 (1955)
99. Henry, J. P., *Orthostasis and the kidney* (Wright Air Development Center, Dayton, Ohio, WADC Technical Report 55–478, 103 pp., Dec., 1955)
100. Henry, J. P., Gauer, O. H., and Sieker, H., *Circulation Research*, **4,** 91–94 (1956)
101. Hetzel, P. S., Swan, H. J. C., and Wood, E. H., *J. Appl. Physiol.*, **7,** 66–72 (1954)
102. Holaday, D. A., and Verosky, M., *J. Lab. Clin. Med.*, **47,** 634–44 (1956)
103. Holling, H. E., MacDonald, I., O'Halloran, J. A., and Venner, A., *J. Appl. Physiol.*, **8,** 249–54 (1955)
104. Holmdahl, M. H., *Acta Chir. Scand.*, Suppl. 212, 128 pp., (1956)

105. Houston, C. S., *New Engl. J. Med.*, **253,** 964–68 (1955)
106. Hubay, C. A., Brecher, G. A., and Clement, F. L., *Surgery*, **38,** 215–27 (1955)
107. Hurtado, A., *Military Med.*, **117,** 272–84 (1955)
108. Jiménez-Vargas, J., Ruz, F., and Jurado, M. D., *Rev. espan. fisiol.*, **11,** 83–104 (1955)
109. Kahn, A., *J. Lab. Clin. Med.*, **46,** 312–17 (1955)
110. Kao, F. F., *Am. J. Physiol.*, **185,** 145–51 (1956)
111. Kao, F. F., Schlig, B. B., and Brooks, C. McC., *J. Appl. Physiol.*, **7,** 379–86 (1955)
112. Kattus, A. A., Rivin, A. U., Cohen, A., and Sofio, G. S., *Circulation*, **11,** 447–55 (1955)
113. Kay, R. H., and Coxon, R. V., *Nature*, **117,** 45–46 (1956)
114. Kleemann, H., Massmann, W., and Sprecher, D., *Zentr. Arbeitsmed. Arbeitsschutz*, **5,** 87–91 (1955)
115. Knipping, H. W., Bolt, W., Venrath, H., Valentin, H., Ludes, H., and Endler, P., *Deut. Med. Wochschr.*, **80,** 1146–47 (1955)
116. Knowles, J. H., Gorlin, R., and Storey, C. F., *J. Am. Med. Assoc.*, **160,** 44–48 (1956)
117. Kolder, H., *Arch. exptl. Pathol. Pharmakol.*, **223,** 486–92 (1954)
118. Kolder, Hj., *Pflügers Arch. ges. Physiol.*, **261,** 583–89 (1955)
119. Kovach, J. C., Paulos, P., and Arabadjis, C., *J. Thoracic Surg.*, **29,** 552–54 (1955)
120. Lambertsen, C. J., Ewing, J. H., Kough, R. H., Gould, R., and Stroud, M. W., 3rd., *J. Appl. Physiol.*, **8,** 255–63 (1955)
121. Lanphier, E. H., *Naval Gun Factory* (Project NS185–005 Subtask 5 Test 4, Formal Report 7–55, 1–37, 1955)
122. Lawther, P. J., and Apthorp, G. H., *Brit. J. Industrial Med.*, **12,** 326–29 (1955)
123. Lee, G. D., and DuBois, A. B., *J. Clin. Invest.*, **34,** 1380–90 (1955)
124. Linderholm, H., and Werneman, H., *Acta. Med. Scand.*, **154,** Suppl. 316, 135–57 (1956)
125. Luft, U. C., and Bancroft, R. W., *J. Aviation Med.*, **27,** 208–20 (1956)
126. Luft, U. C., and Noell, W. K., *J. Appl. Physiol.*, **8,** 444–54 (1956)
127. Luft, U. C., Roorbach, E. H., and MacQuigg, R. E., *Am. Rev. Tuberc. Pulmonary Diseases*, **72,** 465–78 (1955)
128. Luisada, A. A., *Circulation*, **13,** 113–35 (1956)
129. Luisada, A. A., and Cardi, L., *Circulation Research*, **3,** 510–13 (1955)
130. Lundin, G., *Scand. J. Clin. Lab. Invest.*, **7,** Suppl. 20, 39–51 (1955)
131. Margaria, R., and Marro, F., *Exptl. Med. Surg.*, **13,** 249–53 (1955)
132. Martin, C. J., Cline, F., Jr., and Marshall, H., *J. Clin. Invest.*, **34,** 875–78 (1955)
133. Massion, W., *Klin. Wochschr.*, **33,** 457–59 (1955)
134. Mattson, S. B., and Carlens, E., *J. Thoracic Surg.*, **30,** 676–82 (1955)
135. McCubbin, J. W., Green, J. H., Salmoiraghi, G. C., and Page, I. H., *J. Pharmacol. Exptl. Therap.*, **116,** 191–97 (1956)
136. Mead, J., Lindgren, I., and Gaensler, E. A., *J. Clin. Invest.*, **34,** 1005–16 (1955)
137. Metz, B., *Am. J. Physiol.*, **185, 142–44** (1956)
138. Miller, H. C., and Smull, N. W., *Pediatrics*, **16,** 93–103 (1955)
139. Miller, R. D., Fowler, W. S., and Helmholz, H. F., Jr., *J. Lab. Clin. Med.*, **47,** 297–308 (1956)
140. Mochizuki, M., and Bartels, H., *Pflügers Arch. ges. Physiol.*, **261,** 152–61 (1955)

141. Molyneux, L., and Pask, E. A., *Brit. Heart. J.*, **17,** 169–72 (1955)
142. Morgan, D. P., Kao, F., Lim, T. P., and Grodins, F. S., *Am. J. Physiol.*, **183,** 454–58 (1955)
143. Mount, L. E., *J. Physiol.* (*London*), **131,** 393–401 (1956)
144. Nahas, G. C., and L'Allemand, H., *J. Appl. Physiol.*, **8,** 468–72 (1956)
145. Nash, C. B., Davis, F., and Woodbury, R. A., *Am. J. Physiol.*, **185,** 107–12 (1956)
146. Natelson, S., and Menning, C. M., *Clin. Chem.*, **1,** 165–79 (1955)
147. Nickerson, M., and Curry, C. F., *J. Pharmacol. Exptl. Therap.*, **114,** 138–47 (1955)
148. Niden, A. H., and Aviado, D. M., Jr., *Circulation Research*, **4,** 67–73 (1956)
149. Nisell, O. I., and Ehrner, S. G., *J. Appl. Physiol.*, **8,** 565–67 (1956)
150. Otis, A. B., McKerrow, C. B., Bartlett, R. A., Mead, J., McIlroy, M. B., Selverstone, N. J., and Radford, E. P., Jr., *J. Appl. Physiol.*, **8,** 427–43 (1956)
151. Otis, A. B., and Roughton, F. J., *Proc. Roy. Soc.* (*London*), [*B*] **144,** 55–67 (1955)
152. Paintal, A. S., *Quart. J. Exptl. Physiol.*, **40,** 89–111 (1955)
153. Pattle, R. E., *Nature*, **175,** 1125–26 (1955)
154. Peniston, W. H., and Richards, V., *Proc. Soc. Exptl. Biol. Med.*, **90,** 515–57 (1955)
155. Perkins, J. F., Jr., Adams, W. E., and Florens, A., *J. Appl. Physiol.*, **8,** 455–67 (1956)
156. Peters, R. M., *Ann. Surg.*, **142,** 461–67 (1955)
157. Peters, R. M., *Surg. Forum: Clin. Congr. Am. Coll. Surgeons*, **5,** 702–7 (1954–1955)
158. Petty, T., Bartlett, W., and Chapin, J. L., *Proc. Soc. Exptl. Biol. Med.*, **90,** 664–66 (1955)
159. Policard, A., Collet, A., and Giltaire-Ralyte, L., *Comptes rend.*, **241,** 843–44 (1955)
160. Poppell, J. W., Vanamee, P., Roberts, K. E., and Randall, H. T., *J. Lab. Clin. Invest.*, **47,** 885–90 (1956)
161. Price, K. C., Hata, D., and Smith, J. R., *Am. J. Physiol.*, **182,** 183–90 (1955)
162. *Proceedings of the Underwater Physiology Symposium* (National Academy of Sciences—National Research Council, Publication 377., Washington, D. C., 153 pp., 1955)
163. *Pulmonary Circulation and Respiratory Function* (D. C. Thomson & Co., Ltd., Dundee, Scotland, 44 pp., 1956)
164. Rahn, H., and Fenn, W. O., *A Graphical Analysis of the Respiratory Gas Exchange. The O_2–CO_2 Diagram* (The American Physiological Society, Washington, D. C., 38 pp., 1955)
165. Rahn, H., Sadoul, P., Fahri, L. E., and Shapiro, J., *J. Appl. Physiol.*, **8,** 417–26 (1956)
166. Ramos, J. G., and Arjona, P., *Am. J. Physiol.*, **184,** 359–64 (1956)
167. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L., *Am. J. Physiol.*, **185,** 127–32 (1956)
168. Richards, V., and Peniston, W., *Stanford Med. Bull.*, **13,** 484–92 (1955)
169. Roberts, K. E., Poppell, J. W., Vanamee, P., Beals, R., and Randall, H. T., *J. Clin. Invest.*, **35,** 261–66 (1956)
170. Rodbard, S., *Am. Heart. J.*, **51,** 106–26 (1956)

171. Rose, J. C., Freis, E. D., Hufnagel, C. A., and Massullo, E. A., *Am. J. Physiol.*, **182,** 197–202 (1955)
172. Rossier, P. H., and Bühlmann, A., *Physiol. Revs.*, **35,** 860–76 (1955)
173. Rossier, P. H., Bühlmann, A , and Wiesinger, K., *Physiologie und Pathophysiologie der Atmung* (Springer-Verlag, Berlin-Göttingen-Heidelberg, Germany, 330 pp., 1956)
174. Ruhe, C. H. W., and Horn, R. H., *Am. J. Physiol.*, **182,** 325–30 (1955)
175. Sanger, C., Churchill-Davidson, I., and Thomlinson, R. H., *Brit. J. of Anaesthesia*, **27,** 436–46 (1955)
176. Scano, A., *Riv. med. aeronaut.*, **18,** 373–95 (1955)
177. Schaefer, K. E., *J. Appl. Physiol.*, **8,** 524–31 (1956)
178. Schilling, J. A., Harvey, R. B., Becker, E. L., Velasques, T., Wells, G., and Balke, B., *J. Appl. Physiol.*, **8,** 381–87 (1956)
179. Severinghaus, J. W., and Stupfel, M. A., *Anesthésie et analgésie*, **12,** 865–69 (1955)
180. Severinghaus, J. W., and Stupfel, M., *J. Appl. Physiol.*, **8,** 81–87 (1955)
181. Shadle, O. W., Moore, J. C., and Billig, D. M., *Circulation Research*, **3,** 385–89 (1955)
182. Sharpey-Schafer, E. P., *Brit. Med. J.*, **1,** 693–95 (1955)
183. Shepard, R. H., Cohn, J. E., Cohen, G., Armstrong, B. W., Carroll, D. G., Donoso, H., and Riley, R. L., *Am. Rev. Tuberc. Pulmonary Diseases*, **71,** 249–59 (1955)
184. Shephard, R. J., *Flying Personnel Research Committee* (*Great Britain*), Rept. No. 939 (RAF Institute of Aviation Medicine, 21 pp., 1955)
185. Shephard, R. J., *Flying Personnel Research Committee*, (*Great Britain*), Rept. No. 936 (RAF Institute of Aviation Medicine, 5 pp., 1955)
186. Shephard, R. J., *J. Physiol.* (*London*), **129,** 142–58 (1955)
187. Shepherd, J. T., Bowers, D., and Wood, E. H., *J. Appl. Physiol.*, **7,** 629–38 (1955)
188. Simmons, D. H., and Hemingway, A., *J. Appl. Physiol.*, **8,** 95–101 (1955)
189. Singer, R. B., Deering, R. C., and Clark, J. K., *J. Clin. Invest.*, **35,** 245–53 (1956)
190. Singer, R. B., Shohl, J., and Bluemle, D. B., *Clin. Chem.*, **1,** 287–316 (1955)
191. Sisson, G. M., and Fregly, M. J., *J. Appl. Physiol.*, **8,** 128–31 (1955)
192. Sivertson, S. E., and Fowler, W. A., *J. Lab. Clin. Invest.*, **47,** 869–84 (1956)
193. Sjöstrand, T., *Klin. Wochschr.*, **34,** 561–69 (1956)
194. Smith, D. L., Maaske, C. A., and Julian, F., *Am. J. Physiol.*, **181,** 341–46 (1955)
195. Stein, S. N., and Perot, P. L., Jr., *Naval Med. Research Institute Project NM 004 005.09.01*, 759–76 (1955)
196. Steinberg, I., and McClenahan, J., *Am. J. Med.*, **19,** 549–69 (1955)
197. Stewart, P. A., Grossman, H. J., and Kadetz, W., *J. Lab. Clin. Med.*, **46,** 120–27 (1955)
198. Stork, W. J., *Am. J. Roentgenol. Radium Therapy*, **74,** 441–54 (1955)
199. Taylor, D. W., *J. Physiol.* (*London*), **131,** 200–6 (1956)
200. Tenney, S. M., *Anesthesiology*, **17,** 82–87 (1956)
201. Tenney, S. M., and Miller, R. M., *Am. J. Med.*, **19,** 498–508 (1955)
202. Topliff, E. D., and Cullum, L. E., *J. Appl. Physiol.*, **8,** 243–44 (1955)
203. Tsao, M. U., Sethna, S. S., Sloan, C. H., and Wyngarden, L. J., *J. Biol. Chem.*, **217,** 479–88 (1955)

204. Tsao, M. U., and Sloan, C. H., *J. Biol. Chem.*, **216**, 165–77 (1955)
205. Vavala, D. A., *J. Aviation Med.*, **26**, 230–39 (1955)
206. Venrath, H., Lechtenbörger, H., Valentin, H., and Bolt, W., *Z. Kreislaufsforsch.*, **44**, 544–55 (1955)
207. Violette, F., *Comptes rend.*, **241**, 1855–57 (1955)
208. Wégria, R., Capeci, N., Kiss, G., Glaviano, V. V., Keating, J. H., and Hilton, J. G., *Am. J. Med.*, **19**, 509–15 (1955)
209. Weiner, R. S., and Cooper, P., *J. Thoracic Surg.*, **30**, 683–86 (1955)
210. Weyl, R., *Illinois Med. J.*, **108**, 265–69 (1955)
211. Whalen, W. J., *Am. J. Physiol.*, **183**, 445–50 (1955)
212. White, C. S., Lockyear, W. H., and Smith, L. L., *J. Aviation Med.*, **26**, 104–16 (1955)
213. Whittenberger, J. L., *Physiol. Revs.*, **35**, 611–28 (1955)
214. Williams, M. H., Jr., *Am. J. Physiol.*, **184**, 109–12 (1956)
215. Williams, M. H., Jr., *Circulation Research*, **4**, 325–31 (1956)
216. Williams, M. H., Jr., and Towbin, E. J., *Circulatory Research*, **3**, 422–24 (1955)
217. Wilson, R. H., Bruce, E. J., and Hagedorn, M. B., *J. Appl. Physiol.*, **8**, 513–18 (1956)
218. Winterstein, H., *Ergeb. Physiol.*, **48**, 327–528 (1955)
219. Winterstein, H., and Gökhan, N., *Arch. exptl. Phathol. Pharmakol.*, **219**, 192–96 (1953)
220. Witzleb, E., Bartels, H., Budde, H., and Mochizucki, M., *Pflügers Arch. ges. Physiol.*, **261**, 211–18 (1955)
221. Wyss, V., *Riv. med. aeronaut.*, **18**, 732–53 (1955)
222. Young, A. C., *J. Appl. Physiol.*, **8**, 91–94 (1955)

DIGESTIVE SYSTEM[1]

By Sherman Mellinkoff, M.D.
Department of Medicine, University of California at Los Angeles, School of Medicine, Los Angeles, California

According to Schopenhauer, "Man's will in the external world oscillates between frustration and boredom." By the same token review of a tract as long as the digestive system may swing in its functions from a bibliography of much, to a synthesis of little. The former danger will be approached with caution in the first part of this review, and the latter danger embodied recklessly towards the end. The reader is thus forewarned.

Salivary Glands

Relation to thyroid gland.—Clinical reappraisal of a peculiar salivary gland-response to malnutrition was summarized by Sandstead (1). Permanent enlargement of any of the salivary glands may without known functional alteration testify to prolonged inanition long after the latter has been corrected. A possible relationship might be sought in the old observation that submaxillary gland weight increases with thyroid weight in patients with goitre (2), and in the salivary gland hypertrophy caused by treating myxedema with tri-iodothyronine (3).

An excellent index of thyroid function is the ratio of salivary iodide to the protein-bound iodine (4). The ratio is very high in myxedema, apparently because some of the iodide not used by the thyroid gland is excreted in saliva. Watts found renal excretion of I^{131} relatively slow in salivariectomized rats, suggesting some destruction of thyroid hormone by the salivary glands (5). Such a function would be predicted because salivary glands contain tyrosine iodinase. Nevertheless, salivariectomy does not affect the thyroid status of rats (6), and in human beings the salivary uptake of I^{131} is independent of thyroid function (7).

Blood flow.—A neurohumeral mechanism for vasodilation was found in the submaxillary glands of cats (8). Upon stimulation of the chordolingual nerve the glands elaborate a substance that unites with something in plasma to produce a polypeptide resembling bradykinin.

Post-cibal parotid pain after postganglionic superior cervical sympathetectomy was related to vascular congestion (9).

Denervation sensitivity.—Strömblad (10) continues to investigate the denervation sensitivity of the cat's salivary glands to acetylcholine and epinephrine. In denervated glands pilocarpine prevents the usual fall in cholinesterase and amine oxidase, and also the supersensitivity to acetylcholine, epinephrine, and norepinephrine (10, 11). An atropine-like drug, however, increases denervation sensitivity to epinephrine without altering the cholinesterase. Section of the chorda tympani or postganglionic para-

[1] The survey of literature pertaining to this review was completed in June, 1956.

sympathectomy decreases the amine oxidase of the parotid and augments sensitivity of the gland to both epinephrine and norepinephrine. On the other hand, the same degree of hypersensitivity with no change in amine oxidase is produced by preganglionic parasympathectomy or by excision of the superior cervical ganglion (12). Apparently more than one mechanism is involved in denervation sensitivity.

Secretion of saliva.—The sheep's continuous salivary secretion is augmented by parasympathetic stimulation, but sympathetic stimulation causes only a transient increase in salivary flow followed by a fall (13). The sheep's salivary secretory pressure may exceed the arterial pressure within the gland, and, if sodium balance is maintained, the daily salivary volume is about three liters (14). If sodium replacement is not adequate the daily salivary volume falls to two liters, and the potassium content is 12 times higher, the sodium content diminished by two-thirds. In dogs parasympathetic stimulation initially increases transfer of potassium from salivary cells to both blood and saliva (15). After a few minutes salivary potassium concentration stabilizes at a lower level, and potassium moves from blood to cell. Both initial and steady salivary potassium concentrations vary directly with the serum potassium concentration.

Composition of saliva.—In 31 subjects high salivary tryptophane was generally found with relative caries-immunity, and tryptophane *in vitro* created lactobacillus growth with characteristics similar to, but not identical with the growth characteristics of lactobacilli from caries-immune mouths (16).

Human saliva contains small amounts of a plasminogen activator and large amounts of a plasminogen proactivator, but no plasminogen nor trypsin inhibitor (17). Salivary plasminogen proactivator is more plentiful when the glands are not stimulated. Teleologically, the salivary gland fibrinolytic system thus seems designed to prevent plugging of the ducts when flow is least vigorous.

Taste

Application of alkaline solutions to the tongue of a cat produces continuous electrical impulses in the chorda tympani, involving sets of fibres individually activated by water, salt, and quinine respectively (18). "Alkaline taste" seems to be a combination of simpler sensations.

A standardized test of taste discrimination involving identification of 31 foods was used to prove that anosmia dulls the sense of taste (19). Surgical anosmia in five patients did not reduce taste to the low level found in one patient with congenital anosmia (20).

Some individuals can distinguish distilled water from water containing salts in concentrations insufficient to produce an identifiable taste. This property of salts is greater for sodium, magnesium, and calcium than for potassium. Chloride, fluoride, sulfate, and phosphate ions are without a demonstrable effect of this kind (21).

Thirst

Greer (22) produced violent drinking movements in one rat with remote control stimulation through bipolar electrodes implanted in the lateral hypothalamus at the level of the dorsomedian nucleus. It was a chance discovery, but well-documented. The rat drank 400 ml. of water daily when maximally stimulated. Responsiveness was lost by the fifth day.

In dogs the drinking induced by hypertonic saline infusions is inhibited by balloon-distention of the stomach, but only if the distention precedes the infusion by at least 20 minutes (23). Distention immediately prior to the infusion does not inhibit drinking. Once produced, the inhibition persists for an hour after the balloon is deflated. Cocainization of the gastric mucosa prevents the inhibitory effect of distention.

The balloon-distention inhibition of thirst may explain some of Towbin's findings when he measured the water consumption of dogs (24). Each dog seemed to drink a characteristic amount of water at any one time, and to vary his total daily water consumption by changing the number of times he took a drink. Vagotomy increased the size of each drink, and sympathectomy did the opposite.

The Esophagus

Pain.—Baylis *et al.* (25) studied the response of eight normal men and three with coronary artery disease to balloon-distention of the esophagus. They report that pain due to esophageal distention, as compared with the pain of coronary insufficiency, was more likely to be confined to the chest, more rapid in crescendo and decrescendo (10 to 30 seconds), and less often relieved by amyl nitrite. The esophageal pain was associated with contractions in the esophagus and was not accompanied by electrocardiographic changes, even in the three patients subject to angina pectoris. Kramer & Hollander (26), in a similar but more extensive study, found that seven of nineteen patients with Heberden's angina could not distinguish pain caused by esophageal distention from the pain of coronary insufficiency, although the latter changed the electrocardiogram and the former did not. Subjects referred to different areas the pain produced by distention of the same part of the esophagus, but the variability was greater with distention of the midesophagus than with distention of the upper or lower ends.

Motility.—Kramer (27) demonstrated a lower esophageal contractile ring in 6 of 100 persons free of any esophageal symptoms.

Fyke & Code (28) used tiny cylindrical pressure transducers to study the mechanism of swallowing in healthy men and women. At the level of the cricopharyngeal sphincter in the lower end of the pharynx a three cm. band registered a resting pressure about 40 cm. of water higher than the resting pressure in the esophagus. Within one-half second of the act of swallowing the sphincter relaxed, the pharyngeal pressure rose to about 100 cm. of water, and a negative pressure appeared in the upper esophagus.

Hughes (29) isolated the esophageal mucosa in cats, rats, and rabbits and

found species differences in the response of the muscularis mucosae to various drugs. In the cat and rabbit, for example, epinephrine caused contraction or relaxation depending upon the dose and upon the original tone of the preparation, but in the rat only relaxation was observed.

Esophagitis.—Removal of the cardiac sphincter regularly produced esophagitis in dogs whether the esophagogastric anastamosis was above or below the diaphragm (30). Even the Heller procedure (muscle-splitting at the cardia) was followed by esophagitis in five of eight dogs. When the sphincter was left intact and the diaphragm altered to produce a hiatus hernia in five dogs, only one had mild esophagitis in the 25 to 28 week period of observation.

Hightower (31) reviewed the physiology and pathophysiology of the esophagus.

Gastric Motility

Gastroscopy after oral or intramuscular administration of a parasympatholytic drug in healthy volunteers revealed rhythmic contractions of the pylorus and cessation of peristalsis in the body of the stomach (32).

An exchange resin effective in raising the pH of the gastric contents nevertheless had no effect upon the rate at which the stomach emptied itself of barium mixed with cooked cereal in healthy subjects (33). Schapiro & Woodward (34), however, clearly demonstrated inhibition of gastric motility by the multiple-balloon technique shortly after the instillation of HCl into the duodenum or upper jejunum. This effect was present in patients with ulcer as well as those with histamine achlorhydria, and was not mitigated by vagotomy, sympathectomy, or spinal cord transection. Acid in the lower intestine had no effect upon gastric motility. The duration of inhibited gastric motility varied directly with the volume and concentration of acid instilled into the duodenum (35).

Goodman *et al.* (36) had shown by dye-dilution that gastric emptying is delayed in direct proportion to x-radiation dosage when the latter is in toxic ranges. Their observations were confirmed by direct weighing of the stomach contents in rats (37). This effect can be produced by x-ray exposure anywhere in the body, but radiation of the head or abdomen is more potent than the same x-ray dose to the thorax or hindquarters.

Unexplained "flatness" of oral glucose tolerance curves in apparently normal individuals was in no way correlated with the emptying-time of the stomach (38).

Iggo (39) produced ruminal movements in sheep and goats by faradic stimulation of either cut end of the transected vagus nerve. He also recorded electrical activity in nerve fibers coming from receptors in the stomach wall when the latter was distended. In goats and cats electrical activity was recorded in solitary afferent nerve fibres in response to passive distention or active contraction of the stomach (40).

Nalorphine markedly inhibits gastric emptying in man; the effects are quite similar to those of morphine itself (41).

In the dog crushing the left phrenic nerve shortened gastric emptying time and prevented the gastric retention produced by vagotomy (42). Destruction of the right phrenic nerve did not influence the emptying of the pylorus nor of the gall bladder (43).

Gastric Secretion

Basic mechanisms.—White *et al.* (44) infused dogs with neutral red after histamine or mecholyl stimulation of gastric secretion. To avoid artifacts the tissue was prepared for microscopic examination by freezing with liquid nitrogen. It appeared that the indicator was seen only when absorbed by particulate matter, and then only when the secretory rate was very low.

A reduction indicator, triphenyltetrazolium chloride, stains tissues *in vivo* and permits correlation of functional states of the stomach with microscopic appearance (45).

The accumulation of yttrium in various tissues of dogs and rabbits seems to be related to pH and therefore might be helpful in the study of acid secretion (46).

Stern (47) found diamine oxidase in the muscular parts of the rabbit's stomach, but none in the mucosa. He suggests that the muscular effects of histamine depend upon its union with diamine oxidase, a reaction prevented by antihistaminic drugs, whereas, the effects upon gastric acid secretion are not connected with diamine oxidase and therefore not blocked by antihistaminics.

Davenport *et al.* (48, 49) have extended their studies of substances inhibiting the gastric secretion of frogs and mice by attacking the sulfhydryl groups of various enzyme systems. The number of enzymes so affected is large, however, and the authors have decided not to continue this approach to the problem of acid secretion.

Schlesinger, Dennis & Rehm (50) measured a diminished potential difference across the dog's gastric mucosa when secretion was depressed by thiocyanate. Paradoxically the same effect upon potential difference was created by mecholyl or histamine. The authors suggest that thiocyanate may inhibit the cellular anion transport responsible for changes in the potential difference.

Succinic dehydrogenase is plentiful in parietal cells and could conceivably contribute to the energy of acid secretion. Tellkä & Kuusisto (51) found the enzyme concentration increased in rats, mice, and guinea pigs after injection of ACTH, pilocarpine, neostigmine, and caffeine. Alcohol, however, had no influence, nor did atropine and scopolomine. The effects of histamine and insulin were equivocal.

A high incidence of peptic ulcer in patients with pulmonary emphysema (52) renews interest in the relationship between carbon dioxide tension and gastric acid (53).

Nervous and hormonal influences.—Hyperchlorhydria was found in 11 patients with Cushing's syndrome (54). ACTH aggravated gastric ulcers pro-

duced by pitressin injections in rabbits (55). Villarreal, Garrong & Gray (56) noted these effects of ACTH injection in dogs: after a latent period of three to four hours gastric secretion of acid and pepsin increased, and sodium and potassium secretion diminished. These effects were prevented by adrenalectomy, but not by vagotomy, antrectomy, nor administration of diamox in doses sufficient to inhibit histamine-induced secretion of acid.

Woodward *et al.* (57) showed that, in dogs with carefully prepared denervated stomach pouches, alcohol is a powerful stimulus to the formation of gastrin, whether it is applied locally to the gastric antrum or reaches the latter after intravenous injection. They estimate that two-thirds of the acid secretion produced by alcohol is due to the gastrin mechanism and one-third to the intestinal phase of secretion. No appreciable acid secretion was provoked by application of alcohol to the isolated body or fundus of the stomach. Hirshowitz *et al.* (58) noted the alcoholic stimulation of gastrin secretion but believe there is also a central nervous system stimulation of acid secretion mediated by the vagus nerve. This conclusion rests upon the reduction of intravenous alcohol-induced acid secretion by atropine, a similar but lesser reduction by hexamethonium, prevention of such secretion acutely by vagotomy in one dog, and absence of such stimulation in one patient after vagotomy. The possibility, however, would seem to remain that the responsiveness of the antrum to alcohol or of the parietal cells to gastrin was influenced by atropine or vagotomy.

Dragstedt *et al.* (59) reviewed physiological mechanisms of the gastric antrum. Uvnäs *et al.* (60) created mucosal septa between the antrum and the proximal part of the dog's stomach, with anastomosis of the latter to the jejunum. The increased spontaneous acid secretion was very large. An increased responsiveness of the stomach to the secretory effects of insulin supports the view that gastrin in some way augments vagal secretory activity.

Waddell (61) studied six patients before and after removal of the gastric antrum and noted that antrectomy diminished the stimulatory effects of histamine or vagal impulses. He suggests that gastrin exerts a tonic effect upon the central nervous system origins of the vagus nerve, but it seems possible that the locus of the "tonic" effect was the stomach itself. Code & Watkinson (62) suggest that acid in the dog's duodenum regulates gastric acid secretion wholly or mainly through inhibiting vagal impulses. Their septal stomach pouches, however, did not exclude the possibility of duodenal reflux and direct acid-inhibition of the gastrin mechanism.

Acid secretion increases during the first half and diminishes during the last half of the menstrual cycle; chloride and pepsin secretion are not altered (63). Gastric emptying is faster at the time of ovulation.

Eichhorn & Tracktir (64) hypnotized student volunteers to study the effect of emotion upon gastric secretion. Acid and pepsin secretion seemed to rise with contentment and fall with fear or anger.

Eliason (65) in 1952 found a circumscribed region in the anterior part

of the cat's sigmoid gyrus whose electrical stimulation inhibits gastric motor function. Klopper (66) now finds that stimulation of the same zone augments the secretion of HCl.

Effect of drugs.—Kirsner & Ford (67) tested 584 normal individuals and 253 with peptic ulcer and found that 3-beta aminoethyl pyrazole ("histalog") evokes more acid secretion than does histamine at doses productive of much less intense side-effects; the latter were similar, qualitatively, to those of histamine.

Infusions of *Rauwolfia serpentinia* extract (reserpine) increase gastric acid secretion immediately, and this effect is not mitigated by atropine, methantheline bromide (Banthine), nor by epinephrine (68). Orally administered reserpine also provokes acid secretion promptly, but chlorpromazine has no such effect (69). One observer reported no change in the morning basal secretion of gastric acid in 20 patients after taking 1 mgm. of reserpine daily by mouth (70). It is possible that acute and chronic administration of the drug respectively produce different effects, but it seems more likely that the inherent variables in measuring basal acid secretion camouflaged the secretory stimulation.

Kirsner & Ford (71) report increased gastric acid secretion in human subjects after oral or intramuscular administration of phenylbutazone (Butazolidin). The effect is independent of vagotomy or adrenalectomy. In dogs the hyperacidity is found only after oral phenylbutazone, but either oral or intramuscular administration of the drug produces peptic ulcers (72).

Criteria.—A great many workers have investigated the significance of blood pepsin concentration and of uropepsin excretion. Rigler *et al.* (73) found no quantitative correlation between uropepsin and either gastric acid or gastric pepsin secretion; sometimes uropepsin was absent when gastric acid and pepsin were both increased. Generally, however, these workers found uropepsin as well as gastric acid and pepsin secretion diminished by vagotomy, although uropepsin was increased in the immediate postoperative period. Kowalewski & Norvell (74) found a linear relationship between the dose of histamine and the plasma pepsinogen concentration in dogs, and this effect was not mitigated by an antihistaminic nor sodium pentobarbital. Spiro *et al.* (75) report the blood pepsin level generally higher than usual in patients with duodenal ulcer and low after total gastrectomy. Uropepsin excretion tends to be higher in males than in females, higher after adolescence than before, and to diminish somewhat in men after the age of 60 (76). Balfour (77) noted increased uropepsin output in normal male subjects after testosterone administration, especially in older men. The pepsinogen concentration of gastric venous blood was higher than that of the gastric artery in dogs after histamine injection, but no arteriovenous difference was noted in the liver (78). Necheles *et al.* (79) gave 50 mgm. of cortisone daily for 5 to 55 days to six elderly women, one of whom was achlorhydric; only one of the six increased her daily uropepsin output beyond the considerable random daily

variation. Wolfson & Timmis (80), in only four subjects, produced elevations of uropepsin with hydrocortisone but not with cortisone. Gray *et al.* (81) found uropepsin output usually low in pernicious anemia, hypofunction of the adrenals or pituitary, myxedema, total gastrectomy, and gastric cancer. Levy & Levine (82) did not regard uropepsin excretion as a good index of gastric function; they reported only a tendency towards diminished uropepsin after subtotal gastrectomy, and no effect after vagotomy. Two review articles stressed the inexactitude of correlations between uropepsin excretion or blood pepsin concentration and gastric secretory activity (83, 84). Uropepsin and blood pepsin are influenced by renal function; uremia lowers the former and raises the latter (83, 84).

Woodward *et al.* (85) could not correlate tubal gastric analysis with the results by the quinine exchange-resin method except at very low levels of acid secretion, but the latter method did reflect a diminution in gastric acid following vagotomy.

Consequences.—The serum indican concentration and urinary indican output are generally higher in patients with pernicious anemia than in patients with simple achlorhydria, and higher in the latter than in healthy controls (86). In all three groups the indican output is augmented by a low protein diet, suggesting that a difference in the disposition of exogenous protein is not the cause of the high indican levels.

Griffith & Harkins (87) found a species difference in the susceptibility to peptic digestion of the jejunum as compared with the duodenum. The pig's duodenum was relatively more resistant than was the dog's. The authors believe the pig's duodenal mucosa more closely resembles man's and contains a greater density of Brunner's glands, and suggest that the alkaline mucous secretion of the latter in response to secretin or vagal stimulation is a protective mechanism.

Heatley (88) was unable to demonstrate inhibition of the peptic digestion of hemoglobin by gastric mucus. This finding appears to contradict older work (89), but it is possible that the discrepancy is a matter of method. Heatley obtained mucus from pyloric juice exhibiting some peptic activity, and inactivation of the latter may have altered the mucus present. Jennings & Florey (90) used tagged sulfur to demonstrate metabolic differences in mucous-secreting cells of different parts of the stomach. Florey (91) constructively reviews present knowledge of the protective functions of mucin.

Peptic Ulcer

Interest in the relationship between the nervous system and gastric physiology is roused by several articles. Gastromalacia, a gelatinous necrosis without much inflammation in the stomach, was again reported in a patient with poliomyelitis (92). Preoptic lesions in rats caused pulmonary edema and sometimes acute gastric erosions (93). The pulmonary edema was prevented by spinal cord section, but not by vagotomy. The gastric erosions were not

prevented by cord section, but were prevented by vagotomy, although the vagotomized animals did not live long enough to make the latter effect certain. In seven autopsied patients with acute gastric hemorrhage following an acute cerebral vascular accident the predominant lesion in the gastric mucosa was wedge-shaped, suggesting a defect in the mucosal veins, as proposed by Hagemann in 1909 (94).

Kalliomäki (95) was unable to find abnormal glucose or insulin tolerance in a small group of patients with duodenal or gastric ulcers.

Vargas *et al.* (96) demonstrated increased intermedin-like activity in the blood of 22 patients with duodenal ulcer, as compared with 27 normal controls and 21 patients with gastric ulcer. Melanophore stimulation in the Chilean toad was the index used. Age and sex of the patients were not mentioned.

Nielsen (97) summarizes the gastrointestinal accompaniments of hyperparathyroidism, mentioning vomiting, constipation, anorexia, and duodenal ulcer. Tsumori (98) describes a 10 year old boy with both duodenal ulcer and hyperparathyroidism.

Wright *et al.* (99) report a family in which nine of 13 siblings had duodenal ulcers. They found no psychogenic factors to account for this situation. The only one of the 13 siblings who could taste phenylthiourea did not have an ulcer.

Pain.—Woodward & Schapiro (100) were able to prevent the pain produced by duodenal instillation of 0.1 *N* HCl by topical application of local anaesthetics to duodenal ulcers, although the anaesthetics did not affect gastric or duodenal motility. Smith (101) found good but imperfect correlation between the presence of HCl and pain in patients with peptic ulcer, and poor correlation between pain and changes in motility. He concludes that many stimuli, including acid, a jet of food, or a change in tonus, may produce pain by irritating the sensitized area of the ulcer itself.

Intrinsic Factor

Methods of measuring tagged vitamin B_{12} absorption by the radioactive cobalt content of urine, feces, and liver were widely explored (102 to 106). Absorption of vitamin B_{12} is deficient not only in pernicious anemia and after gastrectomy, but also in sprue and in various conditions of the small bowel that promote the growth of abnormal flora, and sometimes to a clinically negligible but measurable degree in older people with hypochlorhydria (107 to 110). The defective B_{12} absorption associated with abnormal intestinal flora can be corrected with antibiotics and may be due to utilization of the vitamin by the bacteria (107, 108). A blind loop of intestine, harboring abnormal flora, may interfere with absorption of either B_{12} or folic acid (111). Halstead, *et al.* (106) summarize the mechanisms of abnormal B_{12} absorption.

Gastrectomized rats will not absorb B_{12} when they are fed hog or human intrinsic factor, but will do so normally if fed rat intrinsic factor (112, 113, 114).

Miscellaneous Aspects of Gastric Physiology

No consistent symptomatology was elicited among 296 patients with various types of spontaneously appearing gastritis (115). Siurala & Tawast (116) found a tendency towards lowered surface tension in the gastric aspirant from patients with mucosal atrophy, suggesting duodenal regurgitation of bile in such individuals.

Friesen *et al.* (117) studied the pyloric myenteric plexus in older individuals and infants with and without hypertrophic pyloric stenosis. Infants have a relatively continuous network of nerve cells, and organization into nests of cells occurs with aging. Among children with hypertrophic pyloric stenosis the individual nerve cells appear immature as compared with those among controls of the same age.

Howard (118) observed diminished gastric motility and acid secretion in soldiers suffering major trauma.

Polak & Pontes (119) found that very large doses of ox bile, sufficient to cause diarrhea, would diminish the increased fecal fat excretion in patients with total gastrectomy, but pancreatin had no such effect. Patients with sprue capable of secreting HCl have gastric mucosal cells similar to those found in pernicious anemia, but it is uncertain whether the abnormality is reversed by vitamin B_{12} or folic acid therapy (120).

Alimentary Absorption and the Small Bowel

Water absorption.—Benson *et al.* (121) used deuterium oxide to measure the absorbed water content of intestinal lymph, portal venous blood, and arterial blood of rats; 99 per cent of the water was absorbed via the portal vein. Grim, Lee & Visscher (122) lavaged canine ileal loops with deuterium-labeled water. The deuterium concentration of the mucosal cells was always higher than that of the luminal fluid, and that of the effluent venous blood lower. The findings suggest two barriers, one of the mucosa and the other in the capillaries. Whole body x-radiation of rats slowed the absorption of water from the small bowel and from the stomach by increasing the blood to lumen exchange and decreasing the converse (123). In the rat's isolated small bowel water absorption cannot occur, even at pressures up to 45 cm. of water, unless glucose is also present in the lumen (124). Lee, Code & Scholer (125) observed no effect upon water absorption from the human stomach by varying salinity from zero to 5.4 per cent; the rate of absorption was about 2.5 per cent of the administered dose per minute. They found water absorption in the small bowel to be 23 per cent of the administered dose per minute for isotonic or hypotonic saline, but diminished somewhat by hypertonic salt.

Electrolyte absorption.—Budolfsen (126) found that potassium inhibits absorption of both sodium and glucose from the rat's small bowel, but has no such effect in the colon. Field *et al.* (127) confirmed their previous observation of a reciprocal effect of sodium and potassium concentrations in the

human ileum, tending to preserve osmolarity of the luminal contents; the colon, however, absorbed most of the sodium presented to it regardless of the potassium concentration. Edelman, Sweet & Nadell (128, 129) found a significant percentage of total body sodium and potassium in the rabbit's intestinal tract. With respect to sodium 2.4 per cent was in the stomach, 1.2 per cent in the small bowel, and 2.1 per cent in the proximal colon. The corresponding figures for potassium were 0.7 per cent, 1.2 per cent, and 4.5 per cent respectively. In rabbits 80 per cent of the extracellular potassium is in the gastrointestinal lumen. In human autopsies the figure was about 33 per cent.

Glucose absorption.—In vitro perfusion experiments with the dog's small bowel show that 50 to 70 per cent of the glucose absorbed from the lumen can be accounted for as either lactic acid or carbon dioxide (130). Anaerobic conditions favor the production of lactic acid. The latter is formed within the intestinal mucosa, but is in higher concentration on the serosal side of the bowel. X-irradiated mice absorb glucose poorly, but this effect is not related to the hexokinase content of the intestine (131). Cummins & Jussila (132) measured glucose and urea absorption from balloon isolated loops of human small bowel. Either substance was absorbed more rapidly by the jejunum than by the ileum. The more concentrated the solution, the more pronounced was the difference.

Fat absorption.—Absorption of olive oil by the rat seems most active in the third quarter of the small bowel, judging by the concentration of radioactive tagged fat in the intestinal wall (133). Baylin *et al.* (134, 135) checked blood radioactivity after feeding normal volunteers either I^{131}-labeled albumin or I^{131}-labeled trioleate to measure protein and fat absorption. The method seemed workable if gastric emptying was checked fluoroscopically. The peak blood level after the protein meal occurred in two hours, and after the fat meal in three hours. Comparable figures for dogs were two and six hours respectively. In an otherwise healthy child with a congenital defect in the thoracic duct and consequent chylothorax, feeding fat changed the composition of chylous fat, but in a manner suggesting that some of the ingested fats were absorbed unchanged and some after hydrolysis (136). Blomstrand (137) in a clear experiment with tagged oleic and palmitic acids found only a small fraction of normal human fecal fat derived from dietary fat; in patients with sprue a large percentage of the fecal fat was dietary in origin. In one patient with steatorrhea due to lymphosarcoma and in another with Whipple's disease the ingestion of nonfat-containing foods increased fecal fat excretion (138). Fat ingestion increased excretion still more, of course. In rats intestinal and thoracic duct lymph contained about the same amount of fatty acids whether the animals fasted or ate fat-free foods (139). The concentration of fatty acids varied inversely with the volume of lymph. Simmonds (140) also found that protein or carbohydrate feeding did not change the fat composition of the rat's thoracic duct lymph. Fat ingestion increased

both the flow rate and the fat concentration of the lymph but did not alter the protein concentration, suggesting some mechanism for accelerating flow other than simple fluid absorption. Tasker (141) reported similar findings and noted no change in lymphatic fat concentration produced by the addition of choline to a fatty meal. In rats with biliary fistulae the intestinal secretion of fatty acids is unchanged despite the steatorrhea (142). Steatorrhea induced by x-radiation, however, promotes a four-fold increase in the intestinal fat secretion without altering the composition of the secreted fat (143). In dogs diversion of bile from the gut causes less steatorrhea than does diversion of pancreatic juice (144). Three patients are described in which it appears that massive diverticulosis of the jejunum was responsible for steatorrhea, as well as the more familiar megaloblastic anemia (145).

Sprue.—Paterson (146) reviews the sprue syndrome. Van De Kamer & Weijers (147) attempt to explain the deleterious effect of gluten upon sprue. An increased amide nitrogen to non-amide nitrogen in the food makes sprue worse, as in feeding gliadin, for example. Feeding glutamine is not harmful. If gliadin is boiled for a short time with *N* HCl it becomes harmless. The authors suggest the possibility that glutamine in some bound form is the offending substance. Mackay & Volwiler (148) used adrenal steroids to produce a dramatic improvement in the percentage of dietary fat, protein, and calcium absorbed in a patient with sprue. The patient was emaciated prior to treatment, and it is difficult to say how much of the improvement was a specific effect upon the absorptive defect and how much was a nonspecific effect of cortisone, perhaps upon nutritional edema in the intestine itself.

Cholesterol absorption.—Lin, Karvinen & Ivy (149) measured cholesterol absorption in rats eating 50 to 288 mg. of cholesterol per 250 gm. of rat daily. The percentage of ingested cholesterol absorbed decreased as a linear function of the dose when the dietary fat was oleic acid. An absorption plateau was reached at 360 mg. per kilo of rat per day. The same authors show that except for triolein the percentage of dietary cholesterol absorbed varies directly with the percentage utilization of the dietary fat (150), and that poorly absorbed plant sterols competitively inhibit cholesterol absorption (151). Byers, Rosenman & Freidman (152) found no change in the intestinal loss of cholesterol or of total lipide in rats made nephrotic by kidney antiserum injections.

Absorption of other substances.—The digestion and absorption of casein by healthy volunteers sharply depressed the blood eosinophile count (153). Gelatin had no such effect. Both proteins produced a very slight fall in the blood sugar concentration and the arterial pressure. The findings suggest specific effects of some amino acids, since casein and gelatin have obviously different amino acid compositions. Whaler's careful *in vitro* studies with labeled amino acids show that rat and cat intestine are capable of carrying out deamination (154). Leucine and valine, but not tryptophane, can be synthesized from the corresponding alpha-oxy acids. It would be of great interest

to know to what extent these reactions serve the purposes of absorption and to what extent reconstitution of intestinal tissue. Active absorption was demonstrated in perfused guinea pig gut for L-isomers of histidine, phenylalanine, alanine, and glycine, but not for their D-isomers, nor for the L-forms of glutamic and aspartic acids (155). Glutamine and aspargenine, however, were actively absorbed by the mucosa, while aspartic and glutamic acids plus ammonia appeared on the serosal side of the preparation. Gruskay & Cooke (156) fed labeled egg albumin to babies and found 4.26 micrograms per liter in the venous blood of normals and a five-fold increase shortly after a bout of diarrhea. Cohn *et al.* (157) fed beef, protein concentrates, or human blood to volunteers. They interpreted the higher blood and urine urea concentrations after the beef or protein concentrate as evidence for poor digestion or absorption of blood. The excretion of urea, however, is not an infallible index of protein absorption, and fecal nitrogen was not measured. In mice a 10-fold adaptive range of fecal iron excretion adjusts to the body stores of iron (158). Oral antibiotics inhibit the intestinal absorption of starch by rabbits (159). Larner & McNickle (160) isolated from the hog's intestinal mucosa an enzyme that hydrolyzes the alpha-1, 6 linkages of isomaltose, panose, and alpha-amylase dextrins.

Carcinoids.—There is a growing and abundant literature on argentiffinomas and their secretion of 5-hydroxytryptamine (serotonin) (161 to 167). Serotonin is excreted in the urine as 5-hydroxyindole acetic acid, and the latter accounts for only 1 per cent of ingested tryptophane in normal subjects, but as much as 60 per cent in patients with metastatic carcinoid (165). One patient developed diarrhea, flushing, dyspnea, cyanosis and other symptoms typical of this syndrome after eating fatty foods, and fat ingestion was found to stimulate the release of serotonin (166).

Motility.—Milton & Smith (168, 169) extended their observations upon electrical activity in the intestine. One cross sectional area near the ampulla of Vater in bitches is a pacemaker for the slow electrical waves that appear to control or accompany rhythmic movement. The pacemaker can be blocked by procaine circumscription, accelerated by heat, or slowed by cooling. Local heating can create ectopic pacemakers. The jejunum is influenced by the duodenal pacemaker and also by one or more subsidiary pacemakers of its own. Generally the slow electrical waves diminish in frequency from the duodenum through the ileum.

Valvular action of the ileocecal valve was observed through a sigmoidoscope in a patient with a cecostomy (170).

Marked relaxation of the rabbit's intestine was produced *in vitro* by concentrations of dilantin well within those attained by therapeutic dosage in epileptics (171). Hence a word of caution in the diagnosis of "abdominal epilepsy" by therapeutic trial.

Autopsy measurements in 65 male and 35 female adults were relatively constant for colonic length (about five and one-half feet), but small bowel

length varied from 11 to 26 feet (172). The status of longitudinal muscle contraction was not determined, but there was a positive correlation between body height and gut length. Aureomycin causes thinning of the small bowel in pigs (173).

The Colon

Motility.—Davidson, Sleisenger & Almy (174, 175, 176) have continued to study pressures in the distal colon. In normal individuals β-methylcholine (mecholyl) sometimes causes relaxation in the rectum and sigmoid and sometimes has no effect, but pressure readings at different levels indicate a similar trend in any one instance. In patients with Hirschprung's disease, however, mecholyl causes no relaxation in the denervated segment even when the normally innervated segment relaxes (174). This apparent violation of Cannon's law is in striking contrast to the effects of mecholyl in achalasia of the esophagus, and may represent a difference between acquired and congenital nerve loss. In normal children broad waves were recorded in the rectum by means of a polyethylene catheter and small, multiple electromanometers (175). The authors suggest that colonic activity should be classified into three wave-types: incoordinate phasic, tonic, and propulsive (176). The latter type is preceded by abolition of the first two.

Garry & Gillespie (177) caused contraction of the rabbit's colon by stimulation of the parasympathetic nerves, and relaxation by stimulation of the sympathetics, but there was great variation in the intensity of these effects depending upon the frequency of the electrical pulse. If both sets of nerves were stimulated simultaneously at low frequency, contraction occurred; at high frequency, the converse.

Flora.—In mice irradiated sufficiently to produce bacteremia the invading organisms are serologically identical to those in the feces (178). Evidence that antibiotically induced changes in the intestinal flora may cause pseudomembranous enterocolitis is accumulating (179). A rather expensive epidemic of this disease occurred in a chinchilla colony; chlortetracycline had been added to the food (180). Pseudomembranous enterocolitis has also been produced in animals by a combination of laparotomy and intra-aortic transfusion of human blood (181). The relationship of these conditions remains to be worked out.

Ulcerative colitis.—Psychiatric aspects of ulcerative colitis are reviewed (182), but a typical example of ulcerative colitis is reported in a Mongolian idiot (183).

Liver and Biliary Tract

Circulation of the liver.—Photocell recording of x-rays beamed through the canine liver after infusion of contrast medium provided a measure of hepatic blood flow (184). Two curves were obtained, one for the arterial and one for the portal venous flow. Brandt *et al.* (185) catheterized the hepatic artery and vein in normal subjects and patients with cirrhosis. In both groups

protein ingestion increased the splanchnic blood flow, oxygen consumption, and arteriovenous oxygen difference, but the changes were less marked in cirrhosis. In neither group was there much change in blood flow or oxygen consumption after feeding glucose. Bishop *et al.* (186) used the same technique to show that patients with rheumatic heart disease have a markedly reduced hepatic blood flow at rest and an even greater reduction after exercise. Andrews *et al.* (187) were able to maintain dog-liver preparations in good condition by perfusion with the animal's own blood. Under these circumstances epinephrine constricted the hepatic artery and portal vein, and in large doses constricted the hepatic vein. The effects of norepinephrine were similar. Acetylcholine dilated the hepatic artery when the latter was constricted, but regularly constricted the hepatic and portal veins. Fisher *et al.* (188) used the Bradley bromsulfalein clearance technique to estimate liver blood flow in anaesthetized and unanaesthetized dogs. Pentobarbital had no effect, and ether augmented hepatic blood flow. Popper and his co-workers (189) demonstrated a rich collateral circulation between the hepatic and phrenic arteries of dogs. Vinyl acetate injected into the hepatic artery regularly caused fatal hepatic necrosis by obstructing direct and collateral circulation, but the same material injected into the portal vein caused passive congestion but little or no necrosis (190).

Reynolds *et al.* (191) demonstrated that wedging a catheter into the human hepatic vein provides a fair index of portal venous pressure. Transcutaneous puncture of the spleen and measurement of pulp-pressure in the latter is also an index of portal venous pressure (192). Pituitrin greatly lowers the portal venous pressure of normal dogs and of dogs with constricted portal veins, and in two patients the drug appeared to arrest bleeding from esophageal varices (193).

Cole *et al.* (194) were unable to confirm accepted views of streamlined flow in the portal venous system. They injected radioactive rose bengal into small veins in the spleen, cecum, small bowel, and left colon of dogs. Counts over right and left lobes of the liver were almost identical in all cases.

Reduction of the dog's body temperature to 24 to 27°C. greatly increased the survival rate after hepatic artery ligation; the hypothermia itself had no apparent adverse effect (195).

Hepatic excretion.—Benemid (*p*-(di-n-propylsulfamyl)-benzoic acid) inhibits hepatic and renal excretion of bromsulfalein (196). Friedman *et al.* (197, 198) perfused the isolated rat liver and found that the liver would take up or excrete into the perfusate cholesterol and cholate depending upon the concentration of these substances in the perfusing fluid. Franklin *et al.* (199) in similar perfusion experiments found that cholesterol removed from the perfusate was secreted into the bile, 10 to 20 per cent of it in the neutral fraction. Friedman, Byers & Omoto (200) cannulated hepatic lymph ducts in living rats. The composition of the lymph was quite similar to that of the kidney (mainly determined by composition of plasma) except that the glu-

cose concentration was high. When the common duct of such an animal was ligated, the volume of lymph rose almost 400 per cent, and its composition reflected hepatic cellular activity. The cholic acid and bilirubin concentrations increased.

Chlorpromazine raises biliary pressure in dogs by increasing resistance at the ampulla of Vater (201). Hollister & Kanter (202) accidentally noted clearing of the serum in a patient with essential lipemia while he was taking chlorpromazine. This observation requires confirmation.

Yamasaki *et al.* (203) measured the "histamine equivalent," or contraction-effect upon the pig's ileum, in the blood of dogs with ligated common ducts. The histamine equivalent rose. They also noted that bile salts mixed with skin inhibit the latter's histaminase. They suggest the combination of histaminase inhibition and increased histamine content causes pruritus.

Despite the depression of bile flow in animals breathing 6 to 9 per cent oxygen, augmentation of flow was easily demonstrable by infusions of desoxycholate (204).

Klatskin & Blumgards (205), by electrophoresis, find both direct and indirect bilirubin in the serum bound to albumin, and believe the Van den Bergh reaction is dependent upon a difference in solubility, not in the protein linkage.

Gall bladder.—Shoemaker, Ulin & Gambescia (206) produced cholecystitis in dogs with intravenous Dakin's solution. Some of these gall bladders concentrated a testing contrast-medium (telepaque) well, but in comparison with controls would not dilate in response to intravenous dehydrocholate. In dogs with Thiry-Vella duodenal loops atropine or hexamethonium relaxed the sphincter of Oddi but did not influence the contractile effect of cholecystokinin upon the gall bladder (207). Procaine locally or hexamethonium systemically, however, did inhibit the release of cholecytokinin by the duodenal mucosa. Jordan reviews (208) the pitfalls in the interpretation of intravenous cholangiography.

Miscellaneous.—Söderstrom (209) produced fetor hepaticus in patients with liver disease by feeding choline. The latter was turned into trimethylamine by intestinal flora, and feeding trimethylamine also produced fetor hepaticus.

Excessive doses of vitamin K appear to deepen the jaundice of infants with icterus neonatorum (210).

In mammals thus far tested the number of hepatic cell mitochondria per gram of liver decreases and the size of the individual mitochondrion increases in proportion to body weight (211). Oxygen consumption *in vitro* is more dependent upon the number of mitochondria than upon the mitochondrial mass.

Lake (212) studied ascites in rats with partially ligated portal veins. Intraperitoneal salt-albumin solution can be carried away at the rate of one-third the rat's body weight per day. Massive infusions of Ringer's solution

produce only a little ascites. These findings are consistent with the fact that extrahepatic human portal hypertension per se rarely if ever causes ascites.

The Pancreas

Magee & Anderson (213) increased the pancreatic manufacture of lipase and protease in rats on a low protein diet by feeding valine. On a 7 per cent casein diet the addition of methionine increased the pancreatic content of lipase and protease, and protease alone rose with phenylalanine or isoleucine-feeding (214). Amylase was not affected, and several other amino acids had no effect.

Grant & Robbins (215, 216) report a new porcine pancreatic enzyme, "pankrin," with proteolytic properties different from those of trypsin or chymotrypsin. Ziffren & Hosie (217) found a collagenase in canine pancreatic juice, and it remains to be compared with pankrin.

Komarov *et al.* (218) using Pavlov-Babkin fistula dogs, found a significant correlation between pancreatic juice enzyme activity of the three major types and protein nitrogen. There was also a significant variation, and it is still not clear how closely the secretion of various enzymes is dependent upon one mechanism.

Kalser & Grossman (219) found a trypsin inhibitor in canine pancreatic juice similar to the one extracted from pancreatic tissue by Kunitz & Northrup. An extract of duodenal mucosa inactivates the inhibitor. Juice rich in trypsin as a consequence of urecholine stimulation is also rich in the trypsin inhibitor.

Serum amylase in the rat is diminished by fasting, partial pancreatectomy, and parenteral ethionine, and both the depot-fat and serum amylase concentrations are increased by a high fat diet (220). A high starch or sucrose diet does not affect the serum amylase but increases the pancreatic tissue amylase. Combat injuries in soldiers, provided they do not directly involve the pancreas, diminish the serum amylase concentration (221). Pleurodynia virus causes pancreatitis in rats, but these animals regenerate pancreatic amylase faster than controls (222).

Although the salivary glands do not secrete lipase, mumps may be accompanied by a high serum lipase without signs of pancreatitis (223). It is suggested that the disease affects the lipase-secreting cells in the crypts of Leiberkühn.

In normal individuals the urinary lipase is between 0.10 to 0.75 units per cc. with no significant alteration by fasting or feeding (224). Lipase, like heparin, will clear lipemic serum *in vitro*, but unlike heparin will not do so in the presence of fluoride or quinine (225). This action of lipase *in vitro* raises the possibility that some inhibitor of its clearing properties contributes to the lipemia sometimes seen in acute pancreatitis, when the serum lipase is elevated.

Thomas and co-workers (226), using unanaesthetized dogs, showed that

bicarbonate concentration is higher when pancreatic juice secretion is rapid. The log of the pancreatic juice bicarbonate concentration plotted against the reciprocal of the secretory rate gives a straight line with a different slope for each dog. The relatively low bicarbonate is secreted at a constant concentration by the acinar cells but is reabsorbed by the ducts when the flow rate is low. Duodenal drainage in human subjects does not reveal variations in bicarbonate, sodium, nor potassium concentrations at different rates of secretion, but in patients with pancreatitis the bicarbonate concentration and the flow rate both fall (227). Diamox decreases the volume of pancreatic juice and its bicarbonate concentration but not the enzyme content (227, 228).

Byers & Friedman (229) found relatively little decrease in cholesterol absorption in the pancreatectomized rat, probably because of the rich supply of cholesterol esterase in this animal's intestinal mucosa.

Rats and mice fed ethionine developed increased stores of total body and hepatic iron (230). In the presence of pancreatic damage the more iron fed, the more absorbed.

Pregnant dogs fed carbon tetrachloride or a methionine-free diet give birth to puppies with pancreatic exocrine deficiency, pulmonary emphysema, and bronchial dilatation, all reminiscent of cystic fibrosis of the pancreas in babies (231). In children with the latter disease creatinuria was diminished by oral or parenteral administration of tocopherol (232).

In 411 human autopsies Cross (233) found numerous small anastomoses between the common bile duct and the pancreatic ductules. In dogs with various surgical procedures causing the liver to secrete bile through the pancreas there was so little pancreatitis produced that one could easily attribute the latter to nonspecific trauma rather than the presence of bile in the pancreatic ducts (234).

Miscellaneous

Bedell *et al.* (235) present a satisfactory method for measuring gas in the gastrointestinal tract by plethysmographic application of Boyle's law. Farrar & Inglefinger (236) demonstrated the feasability of estimating gastrointestinal motility by auscultation.

Castle (237) found a fairly constant time for 5 per cent of a dye-marker fed with oats to be excreted by goats, but considerable variability in the 95 per cent excretion-time. Reynall & Spray (238) used phenol red as an unabsorbed marker, and glucose and iodide as absorbable substances to measure simultaneously in the rat the gastric emptying time, intestinal transit, and gastric and intestinal absorption. The absorption at any level was estimated by the ratio of the phenol red concentration to the concentration of glucose or iodide. Transit in the small bowel was slower as the cecum was approached. One 400 mgm. dose of glucose was completely absorbed by the stomach and the first half of the small bowel.

Appetite and Hunger

The love of Hamlet's mother was so intense that it seemed as though "increase of appetite had grown by what it fed on." So seems the study of appetite itself. Articles on this subject have during the past year appeared at such an accelerating and alarming rate that the reviewer must begin by reviewing reviews.

A symposium on obesity reviews many of the known physical and psychological factors involved (239). Attention is given to Mayer's hypothesis that appetite is regulated by a center in the brain sensitive to glucose utilization, and that the peripheral arteriovenous sugar difference is a good index of satiety (240). The general field of appetite is given wider attention in an editorial in the *Lancet* (241), and by Yudkin (242). Yudkin believes the monotony or satiety produced by any one food insures variety in food choice. A symposium sponsored by the New York Academy of Science (243) includes an excellent, broad-based synthesis of the present status of our knowledge by Grossman; Brobeck's concepts regarding heat-production as a stimulus for satiety; experiments by Janowitz and Hollander showing that dogs adjust their voluntary food intake to the percentage of caloric requirements satisfied by stomach tube; Mayer's stimulating ideas referred to above; and Stunkard's analysis of the "night-eating syndrome" (a pattern of food consumption in some obese individuals).

Dessauer (244) showed that the lizard's consumption of food is proportional to the hours of daylight, when the temperature is constant. Cortisone is capable of augmenting appetite and causing weight loss simultaneously (245). Mayer *et al.* (246) established clinical support for Mayer's experimental observation that exercise in various degrees may diminish or increase food consumption. They found that a sedentary life or very heavy work were both accompanied by a higher food consumption than either light or medium work. Tribe & Gordon (247) found that rats selected food containing the B-vitamins even when deprived of their olfactory bulbs.

Stunkard *et al.* (248) were able to abolish hunger contractions with surreptitious injections of glucagon in seven volunteers. This finding is consistent with Mayer's arteriovenous sugar hypothesis, since glucagon increases this difference. Fryer *et al* (249) found no correlation between the peripheral arteriovenous sugar difference and satiety in normal individuals on various diets. In fact, a high protein diet seemed to provide maximum satiety with a generally lower arteriovenous sugar difference.

Clearly, appetite is a complex feeling influenced by such diverse factors as mechanical sensations in the gastrointestinal tract and television advertisements. It is equally clear, however, that all animals including man have some basic mechanism for regulating food intake that depends in some way upon the food itself. The survival of the species is in a sense *prima facie* evidence for this concept.

It does not seem improbable that this basic mechanism is in some way

connected with the nutrients available to the cells of the body, but it would be surprising if only one of the body's many necessary nutrients were the sole determinant of appetite. The activity of a man no less than that of an ameba is stimulated by the scarcity of any one of a number of accustomed foods.

Unlike sugar, protein is an indispensable food for all higher forms of life. It seems reasonable, therefore, to ask if evolutionary eons have not somehow integrated man's quest for food with the assimilation of protein.

The feeding of a protein meal to normal volunteers creates a reciprocal relationship between the serum amino acid concentration and appetite (250). That this effect is not dependent upon mechanical stimulation of the viscera is suggested by an identical relationship after the infusion of amino acids (250). There is good evidence, however, that the total serum amino acid concentration per se is not an important determinant of appetite. In hepatitis, for example, a disease notorious for anorexia, the postprandial serum amino acid concentration is abnormally low (251, 252, 253). In diabetes mellitus, productive of polyphagia, the fasting serum amino acid concentration tends to be high (254).

The total serum amino acid concentration, however, does not necessarily reflect the concentration of any one amino acid. Consider, for example, two substances having opposite effects upon appetite: insulin and amphetamine. Both of them lower the total blood amino acid concentration, but the blood amino acid patterns produced by the two compounds are quite different (255). Insulin actually raises the concentrations of glycine and serine, while amphetamine does not. Abnormal blood amino acid patterns have been found in patients with hepatic anorexia, although the total amino acid concentration was normal (256). These findings suggest the possibility that the blood amino acid pattern influences appetite.

Besides the well-known minimum requirements for certain amino acids, it is becoming increasingly clear that most, if not all, amino acids supplied in excess are deleterious (257 to 265). But the toxicity of a given amino acid is not static. It is influenced by the simultaneous concentration of other amino acids (260 to 265). That proteins are less expensively used by the body when carbohydrate is served in the same meal (266) is another example of the interdependence of nutrients.

The prudence of Nature has established mechanisms by which the body can successfully supply its cells with an adequate nutrient mixture from food that is not so optimally composed. Rats fed their daily protein requirements in one dose, for example, do not thrive as well as they do when the protein is divided into small portions (267). Nevertheless, they survive. If fat suddenly replaces carbohydrate as the dietary source of adequate calories, nitrogen loss occurs for four days, but thereafter ceases (268).

For simplification, let us assume that the protein mass of the body at one particular time requires for its maintenance 3 amino acids in simple ratio: 1x plus 2y plus 3z. It is probable that this requisite ratio will change with

physiological circumstances and under the influence of various hormones. Now suppose a given meal contains 3x plus 2y plus 1z. The pattern will be altered in the processes of digestion and absorption. The stomach and small bowel feed amino acids to the portal vein at their own pace. The pace is probably suited to the consumption of natural foods and optimal utilization of nutrients. A much higher concentration of blood amino acids is produced by drinking amino acids than by eating an equivalent amount of protein (269), and caloric requirements rise when a given quantity of protein is fed in the form of its constituent amino acids instead of its natural state (270). Let us then assume that the meal enters the portal vein as 2x plus 1y plus 1z. We assume then that the liver will within its finite abilities attempt to deliver the mixture to the systemic circulation in its most desirable form (Fig. 1).

In this scheme it is assumed that the pattern of amino acids available to the cells would in some direct or indirect way influence not only their use, but also the desire for food. It is not assumed, of course, that other chemical factors do not play a similar role.

The "protein mass" in Figure 1 is not a homogeneous unit. There are specialized needs of different tissues. When specialized needs become large enough to be important, it might be expected that a satisfactory amino acid pattern would sometimes be impossible to maintain. This supposition might explain the nausea of pregnancy and the cachexia and anorexia of cancer.

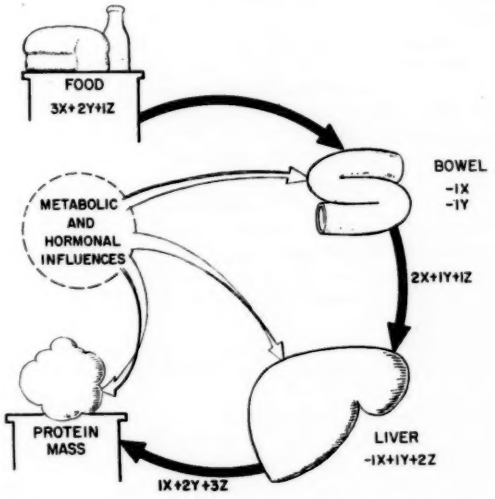

FIG. 1. Schematic representation of intestinal and hepatic alteration of the amino acid composition of food.

The poor appetite associated with gastrectomy might be explained by overloading the small bowel mechanism in Figure 1, and hepatic anorexia by the liver's inability to "correct" the blood amino acid pattern. Severe hepatic anorexia is constantly present, and here it is assumed the liver cannot maintain a normal pattern in the face of ordinary catabolism. In less marked hepatic anorexia, the latter is present only after eating, and, curiously, often most markedly after eating meat or some other high-protein food.

In summary, this hypothesis is an attempt to relate appetite to the major essential nutrient, protein. As the amino acid pattern of food is now known to affect nutrition, the amino acid patterns of extracellular fluids, modified by intestines and liver, are assumed to influence the desire for food.

LITERATURE CITED

1. Sandstead, H. R., Koehm, C. J., and Sessions, S. M., *Am. J. Clin. Nutrition*, **3**, 198–214 (1955)
2. Hämmerli, A., *Deut. Arch. klin. Med.*, **133**, 111–24 (1920)
3. Albright, E. C., Larson, F. C., and Deiss, W. P., *J. Lab. Clin. Med.*, **44**, 762 (1954)
4. Jaimet, C. H., and Thode, H. G., *Can. Med. Assoc., J.* **74**, 865–70 (1956)
5. Watts, R. W. E., *Am. J. Physiol.*, **184**, 365–68 (1956)
6. Newcomer, W. S., *Proc. Soc. Exptl. Biol. Med.*, **91**, 286–88 (1956)
7. Fellinger, K., Hofer, R., and Vetter, H., *Clin. Endocrinol. Metabol.*, **16**, 449–62 (1956)
8. Hilton, S. M., and Lewis, G. P., *J. Physiol.*, **129**, 253–71 (1955)
9. Gardner, W. J., and Abdullah, A. F., *Am. J. Med. Sci.*, **230**, 65–69 (1955)
10. Strömblad, R., *Acta Physiol. Scand.*, **36**, 47–65 (1956)
11. Strömblad, R., *Acta Physiol. Scand.*, **36**, 137–53 (1956)
12. Strömblad, R., *Acta Physiol. Scand.*, **36**, 158–70 (1956)
13. Coats, D. A., Denton, D. A., Goding, R. D., and Wright, R. D., *J. Physiol.*, **131**, 452–62 (1956)
14. Denton, A. A., *J. Physiol.*, **131**, 516–25 (1956)
15. Burgen, A. S. V., *J. Physiol.*, **132**, 20–39 (1956)
16. Green, G. E., Dodd, M. C., and Radike, A. W., *Proc. Soc. Exptl. Biol. Med.*, **91**, 517–20 (1955)
17. Albrechtsen, O. K., and Thaysen, J. H., *Acta Physiol. Scand.*, **35**, 138–45 (1955)
18. Liljestrand, G., and Zotterman, Y., *Acta Physiol. Scand.*, **35**, 380–89 (1956)
19. Clark, E. C., and Dodge, H. W., Jr., *J. Am. Med. Assoc.*, **159**, 1721–23 (1955)
20. Dodge, H. W., Jr., *Proc. Staff Meetings Mayo Clin.*, **31**, 312–14 (1956)
21. Cox, B. J., Nathans, J. W., and Vonau, N., *J. Appl. Physiol.*, **8**, 283–86 (1955)
22. Greer, M. A., *Proc. Soc. Exptl. Biol. Med.*, **89**, 59–62 (1955)
23. Montgomery, A. V., and Holmes, J. H., *Am. J. Physiol.*, **182**, 227–31 (1955)
24. Towbin, E. J., *Am. J. Physiol.*, **182**, 377–82 (1955)
25. Baylis, J. H., Kauntze, R., and Trounze, J. R., *Quart. J. Med.*, **24**, 143–54 (1955)
26. Kramer, P., and Hollander, W., *Gastroenterology*, **29**, 719–43 (1955)
27. Kramer, P., *New Engl. J. Med.*, **254**, 692–94 (1956)
28. Fyke, F. E., Jr., and Code, C. F., *Gastroenterology*, **29**, 24–34 (1955)
29. Hughes, F. B., *J. Physiol.*, **130**, 123–30 (1955)
30. Braasch, J. W., and Ellis, F. H., *Surgery*, **39**, 901–05 (1956)
31. Hightower, N. C., Jr., *Diseases of the Chest*, **28**, 150–69 (1955)
32. Barowsky, H., *Am. J. Gastroenterol.*, **23**, 557–63 (1955)
33. Van Liere, E. J., Northup, D. W., and Canada, W. H., *J. Appl. Physiol.*, **8**, 119–20 (1955)
34. Schapiro, H., and Woodward, E. R., *J. Appl. Physiol.*, **8**, 121–27 (1955)
35. Woodward, E. R., and Schapiro, H., *Proc. Soc. Exptl. Biol. Med.*, **91**, 509–10 (1956)
36. Goodman, R. D., Lewis, A. E., and Schuck, E. A., *Am. J. Physiol.*, **169**, 242–47 (1952)
37. Swift, M. N., Taketa, S. T., and Bond, V. P., *Am. J. Physiol.*, **182**, 479–86 (1955)
38. Test, C. E., Nichols, R. L., Landau, R. L., Ricketts, H. T., and Loughead, R., *Am. J. Med. Sci.*, **231**, 69–74 (1956)

39. Iggo, A., *J. Physiol.*, **131**, 248–56 (1956)
40. Iggo, A., *J. Physiol.*, **128**, 593–607 (1955)
41. Van Liere, E. J., and Northup, D. W., *Proc. Soc. Exptl. Biol. Med.*, **91**, 619–20 (1956)
42. Jefferson, N. C., Dailey, U. J., Walker, L., and Necheles, H., *Am. J. Gastroenterol.*, **25**, 545–49 (1956)
43. Jefferson, N. C., Walker, L., and Necheles, H., *Am. J. Physiol.*, **183**, 237–39 (1955)
44. White, T. D., Swigart, R. A., and Rehm, W. S., *Am. J. Physiol.*, **184**, 453–56 (1956)
45. Békés, M., and Bajusz, E., *Gastroenterologia*, **84**, 164–68 (1955)
46. Dudley, H. C., and Grenberg, J., *J. Lab. Clin. Med.*, **47**, 891–97 (1956)
47. Stern, P., *J. Allergy*, **26**, 268–71 (1955)
48. Davenport, H. W., Chavre, V. J., and Davenport, V. D., *Am. J. Physiol.*, **184**, 1–10 (1956)
49. Davenport, H. W., Chavre, V. J., and Davenport, V. D., *Am. J. Physiol.*, **182**, 221–26 (1955)
50. Schlesinger, H., Dennis, W. H., and Rehm, W. S., *Am. J. Physiol.*, **183**, 75–78 (1955)
51. Telkkä, A., and Kuusisto, A. W., *Ann. Med. Internae. Fenniae*, **44**, 157–63 (1955)
52. Latts, E. M., Cummins, J. F., and Zieve, L., *Arch. Internal Med.*, **97**, 576–84 (1956)
53. Babkin, B. P., *Secretory Mechanism of the Digestive Glands* (Paul B. Hoeber, Inc., New York, N. Y., 1027 pp., 1950)
54. Kyle, J., Logan, J. S., Neill, D. W., and Wellbourn, R. B., *Lancet*, **I**, 664–66 (1956)
55. Crane, W. A. J., and Duncan, I. B. R., *Scot. Med. J.*, **1**, 64–72 (1956)
56. Villarreal, R., Garrong, W. F., Gray, S. J., *Am. J. Physiol.*, **183**, 485–94 (1955)
57. Woodward, E. R., Slotten, D. S., and Tillmans, V. C., *Proc. Soc. Exptl. Biol. Med.*, **89**, 428–31 (1955)
58. Hirschowitz, V. I., Pollard, H. M., Hartwell, S. W., and London, J., *Gastroenterology*, **30**, 244–56 (1956)
59. Dragstedt, L. R., Woodward, E. R., Oberhelman, H. A., Jr., Evans, S. O., Rigler, S. P., Landor, J. H., Dragstedt, L. R., II, and Lyon, E. S., *Arch. Surgery*, **71**, 136–42 (1955)
60. Uvnäs, B., Anderson, S., Elwin, C., and Malm, *Gastroenterology*, **30**, 790–803 (1956)
61. Waddell, W. R., *Ann. Surg.*, **143**, 520–30 (1956)
62. Code, C. F., and Watkinson, G., *J. Physiol.*, **130**, 233–52 (1955)
63. Macdonald, I., *Gastroenterology*, **30**, 602–07 (1956)
64. Eichhorn, R., and Tracktir, J., *Gastroenterology*, **29**, 432–38 (1955)
65. Eliason, S., *Acta Physiol. Scand.*, **22**, Supplement (65 pp.) (1952)
66. Klopper, P. J., *Acta Physiol. Pharmacol. Neer.*, **3**, 420–28 (1954)
67. Kirsner, J. B., and Ford, H., *J. Lab. Clin. Med.*, **46**, 307–11 (1955)
68. Schneider, E. M., and Clark, M. L., *Am. J. Digestive Diseases*, **1**, 22–30 (1956)
69. Haverback, B. J., Stevenson, T. D., Sjoerdsma, A., and Terry, L. L., *Am. J. Med. Sci.*, **230**, 601–04 (1955)
70. Rider, J. A., *Proc. Soc. Exptl. Biol. Med.*, **90**, 636–38 (1955)

71. Kirsner, J. B., and Ford, H., *Gastroenterology*, **29**, 1–17 (1955)
72. Kirsner, J. B., and Ford, H., *Gastroenterology*, **29**, 18–23 (1955)
73. Rigler, S. P., Oberhelman, H. A., Hanke, M. M., and Dragstedt, L. R., *Arch. Surg.*, **71**, 63–67 (1955)
74. Kowalewski, K., and Norvell, S. T., Jr., *Can. J. Biochem.*, **33**, 599–604 (1955)
75. Spiro, H. M., Ryan, A. E., and Jones, C. M., *New Engl. J. Med.*, **253**, 261–66 (1955)
76. Bridgewater, A. B., Sorter, H., and Necheles, H., *Am. J. Gastroenterol.*, **25**, 346–54 (1956)
77. Balfour, D. C., *Am. J. Gastroenterol.*, **25**, 341–45 (1956)
78. Kowalewski, K., Norvell, S. T., Jr., and MacKenzie, W. C., *Can. J. Biochem. Physiol.*, **34**, 244–52 (1956)
79. Necheles, H., Meyer, J., Bridgewater, A. B., Sorter, H., and Wulkan, E., *J. Appl. Physiol.*, **8**, 559–61 (1956)
80. Wolfson, W. Q., and Timmis, G. W., *Clin. Endocrinol. Metabol.*, **15**, 991–94 (Aug. 1955)
81. Gray, S. J., Ramsey, C. G., Reifenstein, R. W., and Krakauer, L. J., *Am. J. Gastroenterol.*, **25**, 532–44 (1956)
82. Levy, A. H., and Levine, S., *Gastroenterology*, **30**, 270–78 (1956)
83. Bauer, H., *Gastroenterologia*, **84**, 283–91 (1955)
84. Spiro, H. M., Ryan, A. E., and Jones, C. M., *Gastroenterology*, **30**, 563–82 (1956)
85. Woodward, E. R., Schapiro, H., and Felts, J., *Surgery*, **39**, 776–79 (1956)
86. Brummer, P., and Kasanen, A., *Acta Med. Scand.*, **152**, 123–28 (1955)
87. Griffith, C. A., and Harkins, H. N., *Ann. Surgery*, **143**, 160–72 (1956)
88. Heatley, N. G., *Quart. J. Exp. Physiol.*, **41**, 25–30 (1956)
89. Ivy, A., Grossman, M., and Bachrach, W., *Peptic Ulcer* (Blakiston, Philadelphia, Penn., 196 pp., 1950)
90. Jennings, M. A., and Florey, H. W., *Quart. J. Exp. Physiol.*, **41**, 131–52 (1956)
91. Florey, H., *Proc. Royal Soc.* (*London*), **143**, 147–58 (1955)
92. Bell, L. G., Thomas, E. E., and Skillicorn, S. A., *Ann. Surg.*, **143**, 106–11 (1956)
93. Maire, F. W., and Patton, H. D., *Am. J. Physiol.*, **184**, 345–50 (1956)
94. Doigand, A., and Shafar, J., *Quart. J. Med.*, **25**, 1–20 (1956)
95. Kalliomäki, L., *Acta Med. Scand.*, **151**, 125–30 (1955)
96. Vargas, L., Orrego, H., and de Feurereisen, L., *Clin. Endocrinol. Metabol.*, **16**, 662–67 (1956)
97. Nielsen, H., *Acta Med. Scand.*, **151**, 359–66 (1955)
98. Tsumori, H., Jensen, E., Hunnicutt, A. J., Foreman, N., and Kinsell, L. W., *Clin. Endocrinol. Metabol.*, **15**, 1141–43 (1955)
99. Wright, J. T., Grant, A., and Jennings, D., *Lancet*, **II**, 1314–18 (1955)
100. Woodward, E. R., and Schapiro, H., *J. Appl. Physiol.*, **8**, 559–61 (1956)
101. Smith, A. W. M., *Quart. J. Med.*, **25**, 393–407 (1956)
102. Schilling, R. F., Clatanoff, D. V., and Korst, D. R., *J. Lab. Clin. Med.*, **45**, 926–34 (1955)
103. Reisner, E. H., Gilbert, J. P., Rosenblum, C., and Morgan, M. C., *Am. J. Clin. Nutrition*, **4**, 134–41 (1956)
104. Ellenbogen, L., Williams, W. L., Rabiner, S. F., and Lichtman, H. C., *Proc. Soc. Exptl. Biol. Med.*, **89**, 357–62 (1955)
105. Glass, G. B. J., Pack, J. T., and Merscheimer, W. L., *Gastroenterology*, **29**, 666–83 (1955)

106. Halstead, J. A., Swenseid, M. E., Lewis, P. M., and Gasster, M., *Gastroenterology*, **30**, 21–36 (1956)
107. Krevans, J. R., Conley, C. L., and Sachs, M. V., *J. Chronic Diseases*, **3**, 234–51 (1956)
108. Halstead, J. A., Lewis, P. M., and Gasster, M., *Am. J. Med.*, **20**, 42–52 (1956)
109. Glass, G. B. J., Goldbloom, A. A., Boyd, L. J., Laughton, R., Rosen, S., and Rich, M., *Am. J. Clin. Nutrition*, **4**, 124–33 (1956)
110. Chow, B. F., Gilbert, J. P., Okuda, K., and Rosenblum, C., *Am. J. Clin. Nutrition*, **4**, 142–46 (1956)
111. Girdwood, R. H., *Quart. J. Med.*, **25**, 87–119 (1956)
112. Nieweg, H. O., Arends, A., Mandema, E., and Castle, W. B., *Proc. Soc. Exptl. Biol. Med.*, **91**, 328–32 (1956)
113. Chow, B. F., Quattlebaum, J. K., Jr., and Rosenblum, C., *Proc. Soc. Exptl. Biol. Med.*, **90**, 279–81 (1955)
114. Watson, G. M., and Florey, H. W., *Brit. J. Exptl. Pathol.*, **36**, 479–86 (1955)
115. Heinkel, K., Elster, K., and Henning, N., *Gastroenterologia*, **83**, 259–83 (1955)
116. Siurala, M., and Tawast, M., *Acta Med. Scand.*, **153**, 451–58 (1956)
117. Friesen, S. R., Boley, J. O., and Miller, D. R., *Surgery*, **39**, 21–29 (1956)
118. Howard, J. M., *Ann. Surg.*, **141**, 342–46 (1955)
119. Polak, M., and Pontes, J. F., *Gastroenterology*, **30**, 489–502 (1956)
120. Gardner, F. H., *J. Lab. Clin. Med.*, **47**, 529–39 (1956)
121. Benson, J. A., Jr., Lee, P. R., Scholer, J. F., Kim, K. S., and Bollman, J. L., *Am. J. Physiol.*, **184**, 441–44 (1956)
122. Grim, E., Lee, J. S., and Visscher, M. B., *Am. J. Physiol.*, **182**, 359–63 (1955)
123. Goodner, C. J., Moore, T. E., Jr., Bowers, J. Z., and Armstrong, W. D., *Am. J. Physiol.*, **183**, 475–84 (1955)
124. Fisher, R. B., *J. Physiol.*, **130**, 655–64 (1955)
125. Lee, P. R., Code, C. F., and Scholer, J. F., *Gastroenterology*, **29**, 1008–16 (1955)
126. Budolfsen, S. E., *Acta Physiol. Scand.*, **33**, 132–36 (1955)
127. Field, H., Swell, L., Dailey, R. E., Trout, E. C., and Boyd, R. S., *Circulation*, **12**, 625–29 (1955)
128. Edelman, I. S., and Sweet, N. J., *J. Clin. Invest.*, **35**, 502–11 (1956)
129. Nadell, J., Sweet, N. J., and Edelman, I. S., *J. Clin. Invest.*, **35**, 512–21 (1956)
130. Newey, H., Smith, E. H., and Whaler, B. C., *J. Physiol.*, **129**, 1–11 (1955)
131. Dickson, H. M., *Am. J. Physiol.*, **182**, 477–78 (1955)
132. Cummins, A. J., and Jussila, R., *Gastroenterology*, **29**, 982–92 (1955)
133. Benson, J. A., Chandler, G. N., Vanstenhuyse, F. E., and Gagnon, J. O., *Gastroenterology*, **30**, 53–61 (1956)
134. Baylin, G. J., Sanders, A. T., Isley, J. K., Shingleton, W. W., Hymans, J. C., Johnston, D. H., and Ruffin, J. M., *Proc. Soc. Exptl. Biol. Med.*, **89**, 51–53 (1955)
135. Baylin, G. J., Sanders, A. T., Isley, J. K., Shingleton, W. W., Hymans, J. C., Johnston, D. H., and Ruffin, J. M., *Proc. Soc. Exptl. Biol. Med.*, **89**, 54–56 (1955)
136. Fernandes, J., van de Kamer, J. H., and Weijers, H. A., *J. Clin. Invest.*, **34**, 1026–36 (1955)
137. Blomstrand, R., *Acta Med. Scand.*, **152**, 127–38 (1955)
138. Crowe, P. J., Blackburn, C. R. B., Mashford, M. L., and Reed, C. S. H., *Australasian Ann. Med.*, **5**, 36–41 (1956)

139. Kim, K. S., Bollman, J. L., and Grindlay, J. H., *Am. J. Physiol.*, **184,** 441–44 (1956)
140. Simmonds, W. J., *Australian J. Exptl. Biol. Med. Sci.*, **33,** 305–13, Part 3 (1955)
141. Tasker, R. R., *Can. J. Biochem. Physiol.*, **33,** 361–67 (1955)
142. Horn, R. G., Blood, F. R., Corrigio, J. G., *Proc. Soc. Exptl. Biol. Med.*, **90,** 258–60 (1955)
143. Morehouse, M. G., and Searcy, R. L., *Science*, **123,** 1032 (1956)
144. Wells, M. H., Shingleton, W. W., and Sanders, A. P., *Proc. Soc. Exptl. Biol. Med.*, **90,** 717–19 (1955)
145. Badenoch, J., Bedford, P. D., and Evans, J. R., *Quart. J. Med.*, **24,** 321–30 (1955)
146. Paterson, J. C. S., *Am. J. Med. Sci.*, **231,** 92–108 (1956)
147. van De Kamer, J. H., and Weijers, H. A., *Acta Paediat.*, **44,** 465–69 (1955)
148. Mackay, I. R., and Volwiler, W., *Gastroenterology*, **28,** 972–80 (1955)
149. Lin, T. M., Karvinen, E., and Ivy, A. C., *Proc. Soc. Exptl. Biol. Med.*, **89,** 422–23 (1955)
150. Ivy, A. C., Tsung-min, L., and Karvinen, E., *Am. J. Physiol.*, **183,** 79–85 (1955)
151. Karvinen, E., and Ivy, A. C., *Am. J. Physiol.*, **183,** 86–90 (1955)
152. Byers, S. O., Rosenman, R. H., and Friedman, M., *Am. J. Physiol.*, **82,** 73–74 (1956)
153. Vartiainen, I., and Apajalahti, J., *Ann. Med. Int. Fenniae*, **44,** 95–98 (1955)
154. Whaler, B. C., *J. Physiol.*, **130,** 278–90 (1955)
155. Fridhanler, L., and Quastel, J. H., *Arch. Biochem. and Biophys.*, **56,** 424–40 (1955)
156. Gruskay, F. L., and Cooke, R. E., *Pediatrics*, **16,** 763–69 (1955)
157. Cohn, T. D., Lane, N., Zuckerman, S., Messinger, N., and Griffith, A., *Am. J. Med. Sci.*, **231,** 394–401 (1956)
158. Shappelle, E., Gabrio, B. W., Stevens, A. R., Jr., and Finch, C. A., *Am. J. Physiol.*, **182,** 390–92 (1955)
159. Stern, P., Hukovic, S., and Fukarek, V., *Gastroenterologia*, **83,** 349–53 (1955)
160. Larner, J., and McNickle, C. M., *J. Biol. Chem.*, **215,** 723–36 (1955)
161. Fraser, I., *Lancet*, **II,** 174–75 (1955)
162. Dockerty, M. B., and Scheifley, C. H., *Am. J. Clin. Path.*, **25,** 770–74 (1955)
163. Dockerty, M. B., *Am. J. Clin. Path.*, **25,** 794–95 (1955)
164. Waldenström, J., and Ljungberg, E., *Acta Med. Scand.*, **152,** 291–331 (1955)
165. Sjoerdsma, A., Weissbach, H., and Undenfriend, S., *Am. J. Med.*, **20,** 520–32 (1956)
166. Bleehen, N. M., *Lancet*, **II,** 1362–63 (1955)
167. Editorial, *Lancet*, **I,** 240 (1956)
168. Milton, G. W., and Smith, A. W. M., *J. Physiol.*, **132,** 100–14 (1956)
169. Armstrong, H. E. O., Milton, G. W., and Smith, A. W. M., *J. Physiol.*, **131,** 147–53 (1956)
170. Ulin, A. W., Shoemaker, W. C., and Deutsch, J., *Arch. Internal. Med.*, **97,** 409–20 (1956)
171. Druckman, R., and Moore, F. J., *Proc. Soc. Exptl. Biol. Med.*, **90,** 173–76 (1955)
172. Underhill, B. M. L., *British Med. J.*, **2,** 1243–46 (1955)
173. Braude, R., Coates, M. E., Davies, M. K., Harrison, G. F., and Mitchell, K. G., *Brit. J. Nutrition*, **9,** 363–68 (1955)

174. Davidson, M. H., Sleisenger, M. H., Steinberg, H., and Almy, T. P., *Gastroenterology*, **29**, 803–24 (1955)
175. Davidson, M. H., Sleisenger, M. H., Almy, T. P., and Levine, S. L., *Pediatrics*, **17**, 807–19 (1956)
176. Davidson, M. H., Sleisenger, M. H., Almy, T. P., and Levine, S. L., *Pediatrics*, **17**, 820–33 (1956)
177. Garry, R. C., and Gillespie, J. S., *J. Physiol.*, **128**, 557–76 (1955)
178. Bradner, W. T., Bernstein, S. E., and McCarthy, R. E., *Proc. Soc. Exptl. Biol. Med.*, **89**, 107–11 (1955)
179. Editorial, *New Engl. J. Med.*, **253**, 201–03 (1955)
180. Wood, J. S., Bennett, I. L., Jr., and Yardley, J. H., *Bull. Johns Hopkins Hosp.*, **98**, 453–63 (1956)
181. McKay, D. G., Hardaway, R. M., Wahle, G. H., Jr., and Hall, R. M., *Arch. Internal Med.*, **95**, 779–87 (1955)
182. Engel, G. L., *Am. J. Med.*, **19**, 231–56 (1955)
183. Lieberthal, M. M., and Frank, H. D., *Gastroenterology*, **28**, 1034–36 (1955)
184. Tornvall, G., and Nordenström, B., *Acta Radiol.*, **43**, 276–83 (1955)
185. Brandt, J. L., Castleman, L., Ruskin, H. D., Greenwald, J., and Kelly, J. J., Jr., *J. Clin. Invest.*, **34**, 1017–25 (1955)
186. Bishop, J. M., Donald, K. W., and Wade, O. L., *J. Clin. Invest.*, **34**, 1114–25 (1955)
187. Andrews, W. H. H., Hecker, R., Maegraith, B. G., and Ritchie, H. D., *J. Physiol.*, **128**, 413–34 (1955)
188. Fisher, B., Russ, C., Selker, R. G., and Fedor, E. J., *Arch. Surg.*, **72**, 600–11 (1956)
189. Jefferson, N. C., Hassan, M. J., Popper, H. L., and Necheles, H., *Am. J. Physiol.*, **184**, 589–92 (1956)
190. Popper, H. L., Jefferson, N. C., Phillips, C. W., Profitt, M. M., and Necheles, H., *Am. J. Physiol.*, **183**, 235–36 (1955)
191. Reynolds, T. B., Balfour, D. C., Jr., Levinson, D. C., Mikkelson, W. P., and Pattison, A. C., *J. Clin. Invest.*, **35**, 213–18 (1955)
192. Atkinson, M., Sherlock, S., and Turner, M. D., *Gastroenterology*, **29**, 370–76 (1955)
193. Kehne, J. H., Hughes, F. A., and Gompertz, M. L., *Surgery*, **39**, 917–25 (1956)
194. Cole, J. W., Krohmer, J., Bonte, F. J., and Schatten, W., *Surgery*, **102**, 543–44 (1956)
195. Bernhard, W. F., McMurrey, J. D., and Curtis, G. W., *New Engl. J. Med.*, **253**, 159–64 (1955)
196. Blondheim, S. H., *J. Appl. Physiol.*, **8**, 529–32 (1955)
197. Friedman, M., Bine, R., Jr., and Ishida, T., *Am. J. Physiol.*, **184**, 412–14 (1956)
198. Burton, S. D., Robbins, E. D., Feigenbaum, L. Z., Friedman, M., Byers, S. O., and Ishida, T., *Am. J. Physiol.*, **182**, 89–91 (1955)
199. Franklin, M. H., Felts, J. M., and Chaikoff. I. L., *Am. J. Physiol.*, **183**, 459–62 (1955)
200. Friedman, M., Byers, S. O., and Omoto, C., *Am. J. Physiol.*, **184**, 11–17 (1956)
201. Menguy, R. B., Grindlay, J. H., and Cain, J. C., *Gastroenterology*, **30**, 752–63 (1956)
202. Hollister, L. E., and Kanter, S. L., *Gastroenterology*, **29**, 1069–76 (1955)
203. Yamasaki, H., Takaoka, T., Akametsu, O., and Ohkura, Y., *Jap. J. Pharmacol.*, **5**, 81–92 (1956)

204. Jalavisto, E., Aantaa, E., Seija, A., and Elosuo, R., *Ann. Med. Exptl. et Biol. Fenniae, (Helsinki)*, **33,** 414–24 (1955)
205. Klatskin, G., and Blumgards, L., *J. Clin. Invest.*, **35,** 537–51 (1956)
206. Shoemaker, W. L., Ulin, A. W., and Gambescia, J. M., *Gastroenterology*, **29,** 1024–36 (1955)
207. Hong, S. S., Magee, D. F., and Crewdson, F., *Gastroenterology*, **30,** 625–30 (1956)
208. Jordan, P. H., Jr., *Surg. Gynecol. Obstet.*, **102,** 218–26 (1956)
209. Soderstrom, N., *Acta Med. Scand.*, **153,** 443–46 (1956)
210. Bound, J. P., and Telfer, T. P., *Lancet*, **I,** 720–22 (1956)
211. Smith, R. E., *Ann. N. Y. Acad. Sci.*, **62,** 403–22 (1956)
212. Lake, B., *Australian J. Exp. Biol. Med. Sci.*, **33,** Part 3, 305–13 (1955)
213. Magee, D. F., and Anderson, E. G., *Am. J. Physiol.*, **181,** 79–82 (1955)
214. Magee, D. F., and Hong, S. S., *Am. J. Physiol.*, **184,** 449–52 (1956)
215. Grant, N. H., and Robbins, J. C., *J. Am. Chem. Soc.*, **77,** 2027–28 (1955)
216. Grant, N. H., and Robbins, J. C., *Proc. Soc. Exptl. Biol. Med.*, **90,** 264–65 (1955)
217. Ziffren, S. E., and Hosie, R. T., *Proc. Soc. Exptl. Biol. Med.*, **90,** 650–52 (1955)
218. Komarov, S. A., Siplet, H., Shay, H., and Guth, P. H., *Am. J. Physiol.*, **183,** 495–509 (1955)
219. Kalser, M. H., and Grossman, M. I., *Gastroenterology*, **29,** 35–45 (1955)
220. Wiberg, G. S., and Tula, J., *Can. J. Biochem. Physiol.*, **33,** 817–25 (1955)
221. Howard, J. M., Frawley, J. P., and Artz, C. P., *Ann. Surg.*, **141,** 337–41 (1955)
222. Dineen, J. K., and Robertson, J. S., *Australian. J. Exp. Biol. Med. Sci.*, **33,** Part 5, 567–78 (1955)
223. Warren, W. R., *Am. J. Med. Sci.*, **230,** 161–68 (1955)
224. Northman, M. H., Pratt, J. H., and Callow, A. D., *Arch. Internal. Med.*, **96,** 188–90 (1955)
225. Holette, C., and Meng, H. C., *Am. J. Physiol.*, **184,** 428–32 (1956)
226. Conly, S., Conden, J. O., and Thomas, J. E., *Am. J. Physiol.*, **182,** 97–99 (1956)
227. Dreiling, D. A., and Janowitz, H. D., *Gastroenterology*, **30,** 382–90 (1956)
228. Watman, R. N., *Surgery*, **39,** 337–39 (1956)
229. Byers, S. O., and Friedman, M., *Am. J. Physiol.*, **182,** 69–72 (1956)
230. Kinney, T. D., Kaufman, N., and Klavins, J., *J. Exptl. Med.*, **102,** 151–56 (1955)
231. Véghelyi, P. V., Sós, J., and Kemény, T. T., *Am. J. Diseases Children* **90,** 28–34 (1955)
232. Nitowsky, H. M., Gordon, H. H., and Tildon, J. T., *Bull. Johns Hopkins Hosp.*, **98,** 361–71 (1956)
233. Cross, K. R., *Am. Med. Assoc. Arch. Pathol.*, **61,** 434–40 (1956)
234. Cross, F. S., Raffuci, F. L., Brackney, E. L., and Wangensteen, O. H., *Proc. Soc. Exptl. Biol. Med.*, **90,** 208–10 (1955)
235. Bedell, G. N., Marshall, R., DuBois, A. B., and Harris, J. H., *J. Clin. Invest.*, **35,** 336–45 (1956)
236. Farrar, J. T. and Inglefinger, F. J., *Gastroenterology*, **29,** 798–802 (1955)
237. Castle, E. J., *British J. Nutrition*, **10,** 15–23 (1956)
238. Reynall, P. C., and Spray, G. H., *J. Physiol.*, **131,** 452–62 (1956)
239. Combined Staff Clinic, *Am. J. Med.*, **19,** 111–25 (1955)
240. Mayer, J., *New Engl. J. Med.*, **249,** 13–16 (1953)
241. Editorial, *Lancet*, **II,** 707–08 (1955)
242. Yudkin, J., *Lancet*, **I,** 645–49 (1956)
243. Hollander, F., *et al.*, *Ann. N. York Acad. Sci.*, **63,** 1–144 (1955)

244. Dessauer, H. C., *Proc. Soc. Exptl. Biol. Med.*, **90**, 524–26 (1955)
245. Kalter, H., *Can. J. Biochem. Physiol.*, **33**, 767, (1955)
246. Mayer, J., Purnima, R., and Kamakhya, P. M., *Am. J. Clin. Nutrition*, **4**, 169–75 (1956)
247. Tribe, D. E., and Gordon, J. G., *Brit. J. Nutrition*, **9**, 1–4 (1955)
248. Stunkard, A. J., Van Itallie, T. B., and Reiss, B. B., *Proc. Soc. Exptl. Biol. Med.*, **89**, 258, (1955)
249. Fryer, J. H., Moore, N. S., Williams, H. H., and Young, C. M., *J. Lab. Clin. Med.*, **45**, 684–96 (1955)
250. Mellinkoff, S. M., Frankland, M., and Greipel, M., *J. Appl. Physiol.*, **8**, 535–38 (1956)
251. Phear, E. A., Ruebner, B., Sherlock, S., and Summerskill, W. H., Jr., *Clin. Sci.*, **15**, 93–117 (1956)
252. Mellinkoff, S. M., Jenden, D. J., and Frankland, M., *Arch. Internal. Med.*, **94**, 604–11 (1954)
253. Mellinkoff, S. M., Boyle, D., and Frankland, M., *J. Lab. Clin. Med.*, **46**, 560–67 (1955)
254. Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*, 806 (Williams and Wilkins, Baltimore, Maryland 1041 pp., 1946)
255. Mellinkoff, S. M., Frankland, M., and Greipel, M., (Unpublished data.)
256. Mellinkoff, S. M., Frankland, M., Greipel, M., and Shibata, H., *Am. Gastroenterol. Assoc. Meeting* (Unpublished data, 1956)
257. *Nutrition Reviews*, **7**, 203–205 (1949)
258. Harper, A. E., Benton, D. A., and Elvehjem, C. A., *Arch. Biochem. and Biophys.*, **57**, 1–2 (1955)
259. Benton, D. A., Harper, A. E., and Elvehjem, C. A., *Arch. Biochem. and Biophys.*, **57**, 13–19 (1955)
260. Gullino, P., Winitz, M., Burnbaum, S. M., Otey, M. C., Cornfield, J., and Greenstein, J., *Arch. Biochem. and Biophys.*, **58**, 253–55 (1955)
261. Greenstein, J. P., Winitz, M., Gullino, P., and Burnbaum, S. M., *Arch. Biochem. and Biophys.*, **59**, 302 (1955)
262. Gullino, P., Winitz, M., Burnbaum, S. M., Otey, M. C., Cornfield, J., and Greenstein, J., *Arch. Biochem. and Biophys.*, **58**, 255–57 (1955)
263. Allison, J. B., *Physiol. Revs.*, **35**, 664–700 (1955)
264. Elvehjem, C. A., *J. Am. Dietet. Assoc.*, **32**, 305–08 (1956)
265. Albanese, A. A., Higgons, R. A., Hyde, G. M., Orto, L., *Am. J. Clin. Nutrition* **4**, 161–68 (1956)
266. Munro, H. N., *J. Nutrition*, **30**, 375–91 (1949)
267. Geiger, E., Rawi, I. E., Thomas, H. V., *J. Nutrition*, **56**, 273–84 (1955)
268. Thomson, W. S. T., and Munro, W. N., *J. Nutrition*, **56**, 139–50 (1955)
269. Mellinkoff, S. M., Boyle, D., Frankland, M., and Greipel, M., *Stanford Med. Bull.*, **13**, 117–24 (1955)
270. Rose, W. C., Coon, M. J., and Lambert, G. F., *J. Biol. Chem.*, **210**, 331–42 (1945)

BLOOD CLOTTING[1]

By Frank D. Mann
Palo Alto Hospital Research Foundation
Palo Alto, California

The past three years have brought rich harvests to every vineyard of coagulation; few have wished to risk a "late harvest."[2] The vintages have many labels and each man prefers his own (Table 1). The reviewer claims only to be an honest taster.

Contributions on most of the topics in coagulation are considered in an order based on the process of coagulation. It seemed best to return to the central attack on the mechanism of coagulation itself which was the theme of the review of Flynn & Coon in Volume 14, of the *Annual Review of Physiology* since the peripheral aspects of the subject were thoroughly reviewed by Jaques in Volume 16. Noteworthy general reviews are those of Alexander (1) and Seegers (2). The abstract reviews of Koller continue to be extremely useful (3). Tocantins has contributed an authoritative monograph on methods of study of coagulation (4). Deutsch has recently presented a meticulous survey of the individual coagulation factors (5); at least one more factor has since appeared and there may well be more before these words are read.

Like this review, coagulation must begin. The classic concept is that the coagulation of blood is initiated by thromboplastin "a clotting protein substance released by platelets as they disintegrate or by tissue cells—" (Webster's New International Dictionary, second edition unabridged, page CXI).

Platelets.—In a thorough study using phase contrast microscopy Erkelens observes the initial formation of fibrin to proceed independently of the platelets and their pseudopodia, which play a vital role in the later formation of the fibrin net (6). Similar observations were made by Tocantins twenty years ago and confirmed by Mann *et al.* in 1949. The paradox that platelets cannot be seen to initiate coagulation appears to be resolved by current studies with the electron microscope. With dark field or phase contrast microscopy the principal changes observed have been in the peripheral hyalomere, the body of the platelet being incompletely visualized. However in 1934 Ferguson wrote: "From the body of the platelet we have seen on one occasion during the earlier phases of alteration a bright particle jerking in and out of the parent element" (7).

Using the electron microscope, Bloom finds that when platelets are

[1] The survey of the literature pertaining to this review was concluded in June, 1956.

[2] "Late harvest," a specific term of wine growing, means deliberately leaving the grapes on the vine until they become overripe. This results in a superior vintage but risks losing the entire crop to frost.

TABLE I

CURRENT TERMS FOR COAGULATION FACTORS, INCLUDING ONLY THOSE KNOWN BY MORE THAN THREE NAMES

Term used in review	Synonyms
Labile factor	Factor V Proaccelerin Ac-globulin
Stable factor	Factor VII Proconvertin Serum prothrombin conversion accelerator (SPCA) precursor Cothromboplastin Autoprothrombin
Antihemophilic factor (AHF)	Thromboplastic plasma component (TPC) Plasma thromboplastin factor A (PTF-A) Antihemophilic factor A Prothromboplastin A Thromboplastinogen Platelet cofactor I Factor VIII
Plasma thromboplastin component (PTC)	Plasma thromboplastin factor B (PTF-B) Antihemophilic factor B Prothromboplastin B Platelet cofactor II Autoprothrombin II Factor IX Christmas factor

exposed to fine quartz particles these are taken up not in the periphery but directly into the central chromomere, causing later disintegration (8). When coagulation is allowed to proceed without the quartz, distinct clear vacuoles corresponding to lost granules are seen in the central chromomere in a number of platelets which are otherwise structurally unchanged (9). D'Antuono & Pieragnoli also note loss of portions of the granulomere while the hyalomere remains intact (10). De Robertis simply states that in the early stages of coagulation morphologically intact platelets act as centers of orientation and condensation of fibrin fibrils (11). Braunsteiner *et al.* (12), also Fieschi (13) make no specific observation regarding early changes in the granulomere. However, Aleksandrowicz *et al.* draw the most far reaching conclusions, namely that pseudopods form from the granulomere, extend through the hyalomere and then break off after which they give rise to the fibrin threads (14). There is considerable agreement and no denial that the

platelets after all may be capable of initiating fibrin formation by early detachment of portions of their central granulomere, while the important function of the peripheral hyalomere remains essentially independent. In agreement with the data from electron microscopy are the isolation experiments of Fonio in which the granulomere and hyalomere were separated and studied separately; the granulomere caused coagulation and the hyalomere retraction of the clot (15). Bessis & Tabuis have succeeded in making motion pictures of platelets using phase contrast microscopy (16). They have made the striking discovery that platelets contain contractile vacuoles; these are usually located in the center of the granulomere and contract actively, a contraction requiring only 15 seconds. Thus far their technique has not permitted a detailed study of the behavior of these vacuoles during coagulation but clearly they provide a mechanism whereby the platelet could expel thromboplastin while remaining morphologically intact.

Communications on fractionation of the coagulation factors in the platelets are in reasonably good agreement where findings overlap. Platelets contain a readily sedimentable component with thromboplastic activity [Jürgens (17), Deutsch (18), Schneider *et al.* (19), Alkjaersig *et al.* (20), Stefanini & Campbell (21), Baserga (22), De Nicola (23)]. Associated with it are labile factor activity and antiheparin activity; the latter may be separable (19, 20). A thromboplastin inhibitor is found in platelets: hence the thromboplastic activity of platelet preparations may increase on dilution [Jürgens (17), Larrieu *et al.* (24)]. Apparently some of the thromboplastin of platelets may persist in serum [O'Brien (25)]. The presence of a material favoring coagulation of fibrinogen and also of a substance itself coagulable are both confirmed [Schneider *et al.* (19)]. A hemorrhagic disease due to deficiency of the thromboplastin of platelets has been described by Van Creveld & Paulssen under the name "thrombopathia hemophilica" (26). These authors, however, isolate a lipide thromboplastin from platelets; it can be separated from antiheparin activity [Van Creveld & Veder (27)]. Several other reports of apparently similar hemorrhagic diathesis have appeared [De Vries *et al.* (28), Soulier *et al.* (29), Neely *et al.* (30)]. Braunsteiner has described in detail the morphology of abnormal platelets as revealed by the electron microscope (31). De Nicola & Rosti have worked out and used extensively a convenient test for thromboplastic activity of platelets (32). Platelet adhesiveness continues to receive study [Savitsky & Werman (33)]. Bounameaux finds that while ACTH or cortisone inhibit platelet adhesiveness when added *in vitro* they may increase it *in vivo* since any increased megakaryocytic activity results in more adhesive platelets (34). Platelets do not normally contain desoxyribonucleic acid but it appears in chronic thrombocytopenic purpura [Lawkowicz *et al.* (35)]. Cronkite and colleagues continue their extensive studies on platelets and irradiation (36). Gregoire finds that heavy doses of x-rays decrease the coagulocytes of insects (37). Platelets contain the ABO blood group antigens [Gurevitch & Nelken

(38), Moureau & Andre (39)], several dehydrogenases [Koppel & Olwin (40)], antifibrinolysin [Stefanini & Murphy (41)], also peptidase, nucleotidase and phosphatase [Salvidio (42)]. Three papers deal with the previously disputed question of agglutination of platelets by thrombin; the findings are by no means uniform but all agree that this phenomenon occurs. [De Robertis *et al.* (43), Bounameaux (44), Desforges & Bigelow (45)]. Justice can hardly be done to the important topic of serotonin and platelets [Zucker & Borelli (46), Bounameaux & Lecomte (47), Fenichel & Seegers (48)]. The same limitation applies to the subjct of abnormal antibodies to platelets [Harrington (49), Stefanini *et al.* (50)]. The findings of Stefanini's group that large transfusions of ordinary bank blood may cause thrombocytopenia is of obvious practical significance (50).

Tissue protein thromboplastin.—Capaldo & Del Buono have well documented the fact that thromboplastic activity of the brain decreases with age (51). Hecht contributes an extensive study on the balance of inhibitor and activator factors in thromboplastin using both lipide and protein material (52). The conditions of the reaction, e.g., preincubation of the plasma with sphingosine sometimes determined whether an inhibiting or an activating effect occurred. Several reports are concerned with the inhibitory effects of high concentrations of thromboplastin [Stein & Abrahams (53), Phillips & Lenahan (54), Walter & Schmutzler (55), Izarn *et al.* (56)]. This effect is more evident with human than with rabbit brain thromboplastin and with dicumarol than with normal plasma. All of the foregoing apply to the perennial problem of standardization of thromboplastic extracts; another large collection of data on this subject is that of Kok (57). These peculiarities of thromboplastic extracts are presumably due to the presence of varying amounts of more or less combined inhibitors and prothrombin conversion factors, to be considered subsequently. Copley reports some peculiar thromboplastin preparations called geloplastins because with their use the fibrin forms a gel (58). Gollub describes further work with a bacterial enzyme preparation called thromboplastinase which destroys all preparations of tissue thromboplastin, but not "blood thromboplastin" (59). Sapuppo studies the thromboplastic activity of aqueous and vitreous humor (60). Von Kaulla concentrates a thromboplastin from urine; it is uncertain whether or not it is of tissue origin (61). It remains a most interesting question under what conditions tissue thromboplastin may gain access to the blood. Kaliampetsos believes that injection of hyaluronidase causes local freeing of tissue thromboplastin (62). Shinowara *et al.* report a large increase in thromboplastic plasma component in acute pancreatitis; the source is undetermined (63). Schneider offers a good summary of the most common undoubted example of entrance of tissue thromboplastin into the blood, namely obstetric shock; the literature on this topic is very extensive (64). Georgatsos *et al.* (65) and Ottaviani *et al.* (66) describe a thromboplastin obtained from erythrocytes. Several reports suggest that it may play a role in hemolytic transfusion reactions [Fogelman *et al.* (67), Niewlarowski & Panasewicz (68), McKay *et al.* (69)].

Lipide thromboplastin.—That the lipide moiety of thromboplastin has activity even after separation from the protein has of course been known for many years; there has been a recent upsurge of interest in this topic. The lipide thromboplastin obtained from platelets by Van Creveld & Paulssen has already been mentioned (26). Using the same method of extraction as Van Creveld & Paulssen, De Vries *et al.* have prepared a lipide thromboplastin from erythrocytes; it also had strong anti-hemolytic properties (70). Leupold has studied both protein and lipide thromboplastin of the erythrocyte; the activity of concentrated suspensions increased markedly on dilution (71), presumably because of inhibitors. Duckert has compared lipide thromboplastin of brain with platelets; the latter seemed to show more inhibitor effect (72). Bell & Alton have used brain lipide (73) and Newlands & Wild soybean lecithin (74) as a substitute for platelets in coagulation tests. Poole finds that chylomicra have thromboplastic activity (75); their surfaces are stabilized by a layer of phospholipide [Robinson (76)]. The effect of lipemia on coagulation remains an interesting unsettled question [O'Brien (77), Manning & Walford (78)].

What is thromboplastin?—The classic theory regards thromboplastin, not as a single substance but as a class of substances, since it is well recognized that platelet, tissue protein, and lipide thromboplastin may all perform the same function, namely to initiate the process of coagulation. The work of the past three years has increased the strength of the classic concept. Thromboplastin is ubiquitous, readily released under the circumstances which lead to clotting and effective in such minute amounts that one can hardly think of any instance of clotting in the body for which one need seek any other initial cause. In the case of clotting *in vitro* there is evidence that sometimes a foreign surface, e.g., glass, may perform the function of thromboplastin i.e., may bring together the reacting coagulation factors [Dick *et al.* (79)]. Evidence also continues to be brought forward that a foreign surface may activate various coagulation factors [Fantl & Hayes (80), Feissly (81), Rapaport *et al.* (82) Biggs *et al.* (83)]. Recently the term thromboplastin has been used to denote a reaction complex of thromboplastin and other coagulation factors [Biggs *et al.* (84)]. This usage would leave no name for the initiator of the entire process.

Prothrombin conversion (cothromboplastic) factors.—Now universally accepted additions to the classic theory of coagulation are the labile and the stable prothrombin conversion factors. These are two plasma factors which react with thromboplastin before prothrombin is converted into thrombin. They are involved in practically all of the abnormalities of coagulation formerly attributed primarily to prothrombin. Both are formed in the liver, as Alagille has recently confirmed (85).

The principal abnormality of the labile factor remains the rare hereditary disease discovered by Owren; it is inherited as a dominant trait involving both sexes according to several reports, e.g., Owen & Cooper (86). Vetter & Vinagger observed labile factor deficiency following radio phosphorus (87). Alkjaersig & Seegers find that labile factor is required for conversion of

prothrombin to thrombin by platelet thromboplastin (88). Cox *et al.* report that labile factor after activation to serum Ac-globulin with thrombin is drastically altered in properties, being now far more readily adsorbable (89). Great adsorbability is characteristic of stable factor, found in most preparations of thrombin.

In contrast to labile factor, stable factor deficiency is by far the most common abnormality of coagulation, being the principal effect of anticoagulants of the dicumarol type. This observation of Hurn *et al.* ten years ago, which was the earliest indication of the existence of the stable factor has been many times confirmed; recent reports are those of Barkham (90), Douglas (91), Jürgens (92), Beaumont & Gele (93), Walker & Hunter (94), Glueck *et al.* (95). The latter workers use a novel assay method involving a synthetic substrate instead of fibrinogen. Congenital deficiency of stable factor, discovered by Alexander, has been the subject of at least eleven recent reports, e.g., Long *et al.* (96). This interesting condition appears to be a trait showing incomplete dominance; a mild form is also noted. Stable factor is decreased to about the same extent as prothrombin in liver disease [Witte & Dirnberger (97)], and also in the blood of the newborn according to several reports, e.g., Passaro (98). There are several reports of increased stable factor in pregnancy, e.g., Alexander *et al.* (99) and one report of a decrease [Hill *et al.* (100)].

Dam & Sondergaard have continued their experiments on the shortening of the prothrombin time resulting from mixing the plasma of vitamin K deficient chicks with that of chicks treated with anticoagulants of the dicumarol type (101). Time relations in the course of the dicumarol treatment are most important; the mutually supplementary effect on mixing is clearly demonstrable only in the initial stage of the dicumarol treatment. This important point is also borne out in the many observations on the human that it is only in the initial or increasing phase of the dicumarol effect that stable factor is decreased far more than prothrombin.

Two distinguished investigators, Quick and Seegers have both been very reluctant to admit the existence of the stable factor. However Quick now believes that to explain the facts one must think in terms of both labile and stable factors as well as of both free and inactive prothrombin (102). Seegers on the other hand finds the concept of stable factor palatable only if it is considered as a derivative of prothrombin, under the name autoprothrombin (103). Physiological evidence suggests that prothrombin is more likely to be a derivative of stable factor than vice versa, if it is essential to think in these terms.

Lewis & Ferguson (104), De Nicola (105), Deutsch & Schaden (106), and Witte & Dirnberger (107) have contributed valuable studies on the characterization, purification and reactions of the stable factor. This substance closely resembles prothrombin but is slightly more adsorbable. Unlike prothrombin it is not converted into thrombin in the systems studied and unlike labile factor it is not used up in the reaction; it is essential for the conversion

reaction and has a great effect on its rate. Owen & McKenzie have shown that stable factor is clearly separable from prothrombin by paper electrophoresis (108).

Antihemophilic factor (AHF).—Thromboplastin, calcium, and the two cothromboplastic factors might well have been regarded as a complete system for the conversion of the prothrombin to thrombin were it not for hemophilia. Numerous studies on this and several closely related diseases have led to the discovery of several other factors all of which have the common characteristic that they appear to be required for the conversion of prothrombin to thrombin by platelet thromboplastin but not by tissue thromboplastin.

Brinkhous and coworkers have continued their noteworthy studies on the antihemophilic factor, AHF, which is deficient in canine and in classic human hemophilia (109, 110, 111). In both species AHF is destroyed very rapidly *in vivo* following intravenous administration, being half gone within two or three hours but it disappeared no more rapidly in hemophilics than in normals, indicating that the disease does not involve excessive destruction of AHF [Langdell *et al.* (111)]. A mild form of human hemophilia is described; it is believed to be an allelic form of the disease [Graham *et al.* (112)]. In mild hemophilia the female conductor is reported to have a subclinical deficiency of AHF. Sjølin reports demonstration of the female conductor by the simple coagulation time (113). Boivin contributes an instructive case of a physician with classic hemophilia who lived past the age of 70 and developed marked generalized arteriosclerosis and myocardial infarction, with recovery (114). Little is known as to what besides hemophilia can influence formation of AHF; Poole & Spaet have found that ethionine causes marked depression of this as well as several other coagulation factors (115). O'Brien reports another instance of severe temporary deficiency of AHF occurring in a woman (116). Preparation of AHF from human plasma is difficult because of its extreme instability; a recent paper on this subject is that of Van Creveld *et al.* (117). AHF is much more stable in certain animal plasmas; in this as in some other respects it resembles labile factor so closely as to suggest that these may be at least closely related molecules. Recent preparations of AHF from animal sources are those of Spaet & Kinsell (118) and of Bidwell (119). The method of Lorand & Laki (120) involves adsorption on kaolin. Murray, Johnson & Seegers have found that certain antihistamines can substitute for AHF in the systems used by them (121); Emmenegger & Lüscher have observed inhibition of coagulation by antihistamines (122).

Plasma thromboplastin component (PTC).—Aggeler and colleagues have further characterized and purified PTC, or as they now term it PTF-B, plasma thromboplastin factor B (123, 124). This factor was first described by Aggeler *et al.* in 1952; it has been the subject of a great many papers, which are in excellent agreement on most points, except that as is usual in coagulation literature different names are used. From several of the more extensive studies it appears that 10 to 20 per cent of cases of hemophilia are due to

PTC deficiency [Soulier & Larrieu (125), Fantl & Sawers (126), Frick (127), Rosenthal (128), Rosenthal (129), Verstraete (130)]. These are clinically indistinguishable from classic hemophilia; the manner of inheritance is the same. However the factor PTC differs sharply from AHF in that it is far more stable and more readily adsorbable and does not disappear from serum after coagulation. The purified preparation of Aggeler *et al.* is a β_2 globulin (124). Owen & McKenzie localized the stable cothromboplastic factor in this same zone (108). Camera has also reported a preparation of PTC (131). Again in striking contrast to AHF, and like stable factor, PTC is decreased by anticoagulants of the dicumarol type [Verstraete (130), Sise *et al.* (132), Naeye (133)]. It is also decreased by vitamin K deficiency (133). Johnson & Seegers believe that PTC also should be considered a derivative of prothrombin; they agree that it is decreased by dicumarol (134). It is clear that while AHF resembles labile factor, PTC resembles stable factor.

Plasma thromboplastin antecedent (PTA).—This factor also has received further study by one of the discoverers, Rosenthal (135) and confirmation [Ramot *et al.* (136)]. From the series previously adverted to it appears that 5 to 10 per cent of cases of hemophilia involve PTA (125 to 130); however Rosenthal believes that numerous mild cases may be overlooked entirely. The disease tends to be milder than classic hemophilia and is inherited as a simple dominant trait, involving both sexes equally. The factor itself lies intermediate between AHF and PTC with regard to adsorbability, precipitability by $(NH_4)_2SO_4$ and stability both *in vitro* and *in vivo*. It is found both in adsorbed plasma and in serum; this permits relatively easy differentiation of PTA from either PTC or AHF deficiency.

Plasma thromboplastin factor D (PTF-D).—Spaet, Aggeler & Kinsel have described a case of mild hemorrhagic diathesis of the hemophilic type in which the plasma coagulability was corrected by AHF, PTC, and PTA deficient plasmas (137). As thus far characterized PTF-D factor appears to be stable on storage but heat labile and not readily adsorbable; it is separable to some extent from the other factors by salt and ethanol fractionation procedures.

Hageman factor.—Of great interest is the discovery by Ratnoff & Colopy of an abnormality in clotting of the hemophilic type entirely without hemorrhagic symptoms (138). The trait is hereditary and involves both sexes. The defective coagulability of the plasma is corrected by plasmas deficient in either AHF, PTC, PTA, or PTF-D. Hageman factor is sharply differentiated from all other known coagulation factors by its presence in aged human serum which has been adsorbed with $BaSO_4$. Despite the stability of the factor *in vitro*, correction of the defect by transfusion lasted only 16 hours. The paper of Ratnoff & Colopy involves three patients, one of them entirely unrelated to the other two. It had been in the literature only a few months when the careful study of two similar cases by Frick & Hagen appeared (139). The reviewer now recalls puzzling over a similar case in 1948, without reaching any understanding. It sometimes appears that the most confusing

names may gain recognition simply by attracting attention amid the welter of others, e.g., Christmas disease, which has nothing to do with Christmas. It might be justifiable to call attention to this fascinating condition, Hageman trait by such a name as "hemophilia sine hemophilia."

There must be some lesson to be learned from the finding of a defect of coagulation which in the laboratory appears as severe as classic hemophilia but in the patient does not even complicate major operations. Along the same line, Bell *et al.* have found that the normal horse may be considered to be in a hemophilioid state, yet they very seldom develop hemarthroses, despite their obvious opportunities (140). The reviewer's interpretation is that these facts speak for the importance of tissue thromboplastin in normal hemostasis and also for the importance of inhibitors in the hemorrhagic diseases of the hemophilic type.

Factor X.—Factor X is included in the class of factors required by platelet but not by tissue thromboplastin, although lack of it has not thus far been associated with hemophilia-like disease. This factor has been described by Koller's group on the basis of their finding that reactivity of serum with platelets is decreased by anticoagulants of the dicumarol type in a manner independent of the action of these agents on reactivity to tissue thromboplastin, i.e., reduction of stable factor, and also independent of their action on PTC [Duckert *et al.* (141)]. These differences are based on the *in vivo* kinetics of the action of the anticoagulant, in that Factor X is affected before PTC and also on the *in vitro* kinetics of the reactions of the various serum mixtures on the platelets: Factor X is found to govern more the speed of the reactions, PTC the total activity which develops. Rather similar findings are reported by Walker & Hunter; they are not quite so definite in their conclusions (142). Beller & Mammen describe a factor which is deficient in the blood of the newborn and in dicumarol blood; they believe that it differs from PTC but is identical with both Factor X and PTA (143). On the other hand, Fiehrer *et al.* agree with Koller that Factor X differs from both PTC and PTA (144). According to Koller's group Factor X resembles PTC and stable factor in being a stable, highly adsorbable substance found in serum, but is separable from these other two factors by chromatography and differential adsorption (141).

The important questions as to whether any of the foregoing six factors are identical and as to the role of inhibitors in hemophilioid disease remain for subsequent consideration.

Formation of prothrombin.—Lasch & Roka describe the formation of prothrombin in a cell-free system of hepatic mitochondria (145). Oxygen was required and the optimum pH was 7.9. Prothrombin seemed to be formed from stable factor since aged serum was the best substrate and stable factor activity decreased sharply as prothrombin appeared. Dicumarol did not inhibit this reaction *in vitro* but mitochondria from rats which had received large doses of dicumarol did not form prothrombin even when vitamin K was added. In another paper the same authors report that while the

formation of prothrombin from stable factor was accomplished by frozen or even dried mitochondria, strictly fresh hepatic mitochondria were required to form stable factor itself; the substrate was fresh plasma freed of both stable factor and prothrombin (146). The labile factor content of the system did not diminish while large amounts of stable factor formed, Similarly fresh mitochondria from heart, spleen, kidney, brain, bone marrow, and lung could not bring about formation of stable factor under the same conditions.

One hypothesis presented with this admirable work cannot yet be integrated with knowledge from other sources. The authors believe that a cycle exists, involving the formation of prothrombin from stable factor in the liver and of stable factor from prothrombin by the process of coagulation in the peripheral circulation. This is an attractive idea, particularly in view of the well known rapidity of physiologic turnover of these substances. However these authors present no evidence that stable factor forms from prothrombin during coagulation, a concept by no means universally accepted. The reviewer thinks otherwise because the stable factor is very low in the serum from the blood of individuals in the initial phase of the effect of dicumarol, although nearly a normal amount of prothrombin has been converted into thrombin during coagulation of this blood. Duckert *et al.* found the stable factor content of normal serum to be the same as that of plasma (147). In the intact body dicumarol characteristically causes stable factor to decrease much faster than prothrombin; then on recovery stable factor increases faster than prothrombin. In congenital deficiency of stable factor prothrombin is normal and stable factor does not form on coagulation of such blood although prothrombin is eventually consumed. Finally there is the very rare abnormality, true hypoprothrombinemia, in which prothrombin is very low and stable factor nearly normal [Biggs & Douglas (148)]. There would seem to be ample evidence that stable factor and prothrombin are independent physiologic variables although the substances are interconvertible under appropriate circumstances.

Alkjaersig & Seegers (149) have confirmed the formation of prothrombin from stable factor by hepatic mitochondria as shown by Lasch & Roka. Less exciting but welcome is the paper of Alagille reemphasizing the importance of the liver in the formation of prothrombin and the ineffectiveness of vitamin K, including K_1 in the hypoprothrombinemia of liver disease (85). However Witte & Dirnberger believe prothrombin and labile factor may form in the bone marrow (150). There are two further confirmations of the old but significant observation that in liver disease prothrombin is often decreased more than the prothrombin time would indicate [Forell & Koller (151), Hunter & Walker (152)]. Jaques has reviewed the physiology of the dicumarol anticoagulants (153) and Jaques *et al.* the metabolism of the K-vitamins (154).

Composition and reactions of prothrombin.—Carter & Warner have brought forward the interesting idea of a protein moiety common to stable factor, prothrombin, and thrombin (155). This concept is based on the finding that

these three substances have the same content of disulfide bonds. Several studies on the amino acid composition of prothrombin have appeared [Ray *et al.* (156), Laki *et al.* (157)]. Milstone prepares prothrombin by chromatography on columns of diatomaceous earth; the objective in the use of this method is the elimination of other coagulation factors (158). The best prothrombin preparation obtained by this technique failed to produce thrombin when treated with cephalin and calcium for 28 hours.

Seegers and his group have continued their extensive studies on the changes prothrombin undergoes in concentrated citrate solutions (159 to 165). Exposure to the citrate causes nearly half of the nitrogen and most of the carbohydrate of the prothrombin to split off as fragments soluble in trichloracetic acid. Miller & Seegers (161) isolate a polysaccharide liberated in this process and find it to be a polymer of glucose. It contains no glucosamine, although glucosamine is liberated at the same time. The polymer has no heparin-like activity. This chemical alteration results first in a substance having the biologic activity of stable factor; it restores the coagulability of the plasma of congenital stable factor deficiency. This substance is termed citrate autoprothrombin. On further treatment with citrate it acquires thrombin activity and is called citrate thrombin. On treatment of prothrombin with the thromboplastin-calcium conversion system, thrombin forms without this profound chemical alteration and without the appearance of nitrogenous and carbohydrate products soluble in tricholoracetic acid. This thrombin is called biothrombin; by treatment with concentrated citrate it can be converted into citrate thrombin without loss of activity. When the prothrombin is allowed to react with platelet thromboplastin, calcium and a small amount of labile factor, an autoprothrombin product forms with only partial loss of nitrogen and carbohydrate; this is convertible to citrate autoprothrombin by treatment with concentrated citrate. Finally when prothrombin is allowed to react with thrombin yet another product forms which is called autoprothrombin II and is thought to have the activity of PTC.

There were of course, from the very first, strong indications of close chemical and physiological interrelationships between prothrombin and stable factor and this resemblance clearly extended to PTC when this factor came into the picture. Accordingly the chemical basis for this relationship brought forward by Carter & Warner, as well as the interconvertibilities demonstrated by Seegers *et al.* are of great interest. This work in no way contradicts the evidence from a score of laboratories that assigns these closely related substances distinct individual roles in the process of coagulation. To rename stable factor "autoprothrombin" would be like renaming glycogen "autoglucose."

Milstone uses the term "thrombokinase" to indicate a substance which converts prothrombin to thrombin without requiring calcium. Unlike thromboplastin, thrombokinase is not sedimentable at 85,000 g. Thrombokinase is inhibited by soy bean trypsin inhibitor and is believed to be a proteolytic

enzyme. In a recent interesting study Milstone finds that when to thrombokinase are added cephalin plus an accelerator reagent, which is adsorbed from bovine serum with $BaCO_3$, the rate of conversion of prothrombin to thrombin is multiplied by 100 times or more, but for this more rapid conversion calcium is required (166). If thrombokinase contained a little labile factor and the accelerator reagent a little stable factor the usual complete thromboplastin conversion system would be present. The reviewer personally finds it helpful to think of Milstone's thrombokinase and also the citrate conversion mechanism as interesting alternatives to the usual conversion of prothrombin to thrombin by the thromboplastin system; perhaps all of them are basically proteolytic reactions. Alkjaersig *et al.* find that soy bean trypsin inhibitor also blocks formation of thrombin by citrate (167). Trypsin itself will convert prothrombin to thrombin [Kleinfeld & Habif (168)]. Thrombin will react with prothrombin to form additional thrombin. Alkjaersig *et al.* find that the thrombin formed by the action of thrombin or trypsin is a product of relatively low molecular weight resembling citrate thrombin (167). With respect to physiological significance it should be remembered that the thromboplastin conversion system requires seconds while these mechanisms require hours.

Thrombin and its reaction with fibrinogen.—Sherry *et al.* have summarized their evidence that thrombin acts as a proteolytic enzyme (169). Bagby & Szara find that in addition to the fibrinopeptide of Lorand, a carbohydrate residue is liberated from fibrinogen by the action of thrombin (170). This explains their previous observation that fibrin has a lower hexose content than fibrinogen (171). Bailey & Bettelheim demonstrate two different polypeptides liberated during the clotting of fibrinogen; only one contains glutamic acid (172, 173).

De Vries *et al.* find that synthetic basic-polyamino acids accelerate the clotting of fibrinogen much as protamine does (174). In three cases of severe hypocalcemia, Fanconi observed prolonged coagulation times when the serum calcium was in the range 3 to 4 mg. per 100 ml. (175). When the serum calcium was restored to normal, the coagulation time was also normal. It seems likely that this effect concerned the thrombin-fibrinogen reaction, although this is not certain. From a careful study of the accelerating effect of calcium on the clotting of fibrinogen Ratnoff & Potts conclude that this activity is due to calcium adsorbed on the fibrinogen (176). This is in agreement with the interpretation of Craddock *et al.* that an abnormal protein of multiple myeloma impairs the clotting of fibrinogen by interfering with the participation of the calcium ion in the reaction (177). Further contributions on protein inhibitors in multiple myeloma are those of Frick (178) and Gemacher *et al.* (179). Ratnoff restudies the factor he has previously named "thrombin accelerator" and now regards this name as inappropriate since it is uncertain whether it acts on thrombin or on fibrinogen (180). At any rate it appears to be an actual factor in plasma or serum having the property of accelerating the conversion of fibrinogen to fibrin by thrombin; this factor is deficient in liver disease and eclampsia.

Fibrinogen and fibrinolysin.—Kekwick *et al.* describe the purification of human fibrinogen, using systems containing diethyl ether. The product is more than 97 per cent clottable, free of plasminogen and plasmin, and homogeneous in the ultracentrifuge (181). Sheppard & Wright have continued their studies on the zeta potential at fibrinogen-solid interfaces (182). The fibrinogen is tenaciously bound on surfaces of Pyrex or Teflon. The zeta potential decreases as protein concentration increases. Heparin increases the zeta potential. Unclotted thrombin-fibrinogen mixtures also have a higher zeta potential than the fibrinogen alone. Rieser finds that exposure to x-rays *in vitro* decreases the coagulability of fibrinogen; the effect is not prevented by sulfhydryl reagents (183). Burstein & Guinand have restudied the increased coagulability of fibrinogen induced by heat (184). The same authors show that the changes in pH, calcium, salts, and urea affect the coagulability of fibrinogen characteristically to different degrees in different animal species (185). They further observe that horse or pig fibrinogen prolongs the thrombin time of human plasma (186). Burstein *et al.* also find that human fetal fibrinogen produces a peculiar translucent clot which is less readily compressible than the adult clot (187). Greene observes that clot retraction involves no change in the width of the fibrin strands but rather the drawing together of the strands by the platelets (188). Ingram presents evidence of variations in fibrinogen itself, which affect its coagulability (189). Lyons believes that there is a complex of prothrombin and fibrinogen, which splits on clotting (190).

Guest describes methods for the individual assay of profibrinolysin and antifibrinolysin of plasma, also urinary fibrinolysin (191). Neoplasm caused a slight increase, pregnancy a much larger increase in both pro and antifibrinolysin of plasma. Sherry reports that when human profibrinolysin is activated with streptokinase, and bovine fibrinogen used in the assay the results are spuriously high due to activation of contaminating bovine profibrinolysin (192). Ratnoff observes that active fibrinolysin dissolves fibrin and renders fibrinogen incoagulable at approximately the same rate (193). Further communications have appeared on fibrinolysin in cirrhosis [Kwaan *et al.* (194)] and prostatic carcinoma [Dolaz *et al.* (195)] and in obstetric complications [Malagamba (196)]. Obersteg presents an extensive study of the behavior of the blood after death (197). In experiments on dogs and cats, the blood was found to remain fluid but coagulable about three hours after sudden death; it then became completely incoagulable due to fibrinolysis.

Fearnley & Lackner describe a labile fibrinolysin in normal blood (198). It rapidly disappears from fluid blood and plasma kept at room temperature; therefore to preserve its activity the specimen is rapidly chilled. This labile fibrinolysin is increased by moderate activity such as walking; it is greatly increased by injection of adrenalin.

Antithrombin.—There is no reason to believe that the inactivation of thrombin is any simpler than its activation. Seegers *et al.* have named four antithrombins by the numbers one through four (199, 200). Antithrombin I is simply fibrin. Quick has also previously credited fibrin with a role in the

inactivation of thrombin and continues to emphasize its significance (201). The current findings of Wenckert are similar (202). Seegers' antithrombin III has the property of inactivating laboratory preparations of thrombin. By the classic procedure of shaking with ether this property is removed; therefore antithrombin III is destroyed. Antithrombin IV cannot inactivate laboratory thrombin; its arises in the ether-treated plasma concomitant with thrombin formation in such plasma and inactivates this thrombin. Thrombin newly formed in plasma, whether ether-treated or not, is enormously more susceptable to inactivation by antithrombin than are laboratory preparations of thrombin. Seegers discusses the difficulties this causes in the study of antithrombin (199). To conclude the scheme, antithrombin II is the cofactor of heparin. Monkhouse *et al.* report the adsorption of antithrombin and heparin cofactor on aluminum hydroxide (203). Fitzgerald & Waugh present a study of heparin cofactor from bovine plasma (204). In another paper Waugh & Fitzgerald conclude on the basis of calculations made from the data of other investigators that heparin cofactor does not exist independent of antithrombin (205). Burstein reaches the same conclusions from his experimental data (206). Burstein and Guinand make the interesting observation that heparin increases the amount of antithrombin destroyed in the process of inactivation of a given amount of thrombin (207). The rate of inactivation is also increased. In general the more thrombin is inactivated, the more antithrombin is also consumed. Chevallier *et al.* report a unique case of elevation of antithrombin in thrombocytopenic purpura (208). There was no increase in antithromboplastin. Jürgens observes increased antithrombin in epidemic hepatitis (209).

Heparin.—In the many years that have elapsed since the formulation of Howell's theory it has not been decided whether or not heparin acts as a physiological anticoagulant. Brambel *et al.* present a far-reaching hypothesis assigning heparin a central role in homeostasis (210). Douglas finds that heparin affects principally the conversion of prothrombin to thrombin rather than the reaction of thrombin with fibrinogen (211). Freeman *et al.* (212, 213) and also Nilson & Wenckert report on the basis of new methods that there are readily measurable amounts of heparin in normal blood (214). Wenckert & Nilson believe that prothrombin is a firm complex of thrombin and heparin, which is split by Russell viper venom, liberating thrombin and heparin (215). The function of thromboplastin is supposed to be the neutralization of this liberated heparin. Bragdon & Havel report a heparin-like action of various polyvalent inorganic anions; this should be borne in mind when performing heparin assays on blood specimens after precipitating proteins with such anions (216). Terzioglu & Ozer report that cold-induced hibernation increases blood heparin, while prolonged drug narcosis does not (217). Without concluding that heparin is the explanation, several other papers on decreased coagulability in hibernation should be noted [Raths & Perlick (218)], Perlick (219), Smith *et al.* (220)].

Antithromboplastin.—In reviewing the literature, it is necessary to con-

sider hemophilia as a deficiency of AHF, since this is the point of view of most investigators. The other theory, that hemophilia involves primarily excess antithromboplastin, is backed by much unrefuted evidence. It is summarized in a brief paper by Tocantins, the originator (221). Tocantins' finding that the coagulability of hemophilic plasma is increased by dilution is fully confirmed by Chevallier *et al.* (222). Also in agreement with Tocantins, Chevallier *et al.* find that the dilution curve of the coagulation time of hemophilic blood is never completely normalized by transfusion, because of the inhibitor present. Johnson finds that after extraction with ether, hemophilic plasma will activate purified prothrombin (223). A lipide inhibitor is found in the upper layer of plasma on ultracentrifugation [Johnson *et al.* (224)]. On coagulation, AHF is believed to be neutralized by conjugation with lipide inhibitor, which is removed by extraction with ether [Johnson & Seegers (225)]. Excess antithromboplastin has also been observed in PTC and PTA deficiencies [Chevallier *et al.* (226), Fiehrer *et al.* (144)]. Chevallier *et al.* believe that hemophilia involves excess antithromboplastin together with deficiency of coagulation factors (222). Rapaport *et al.* compare the lipide antithromboplastin of brain with soy bean phosphatide (227). Seegers *et al.* believe it may play a role in the failure of brain thromboplastin plus platelets plus calcium to convert purified prothrombin to thrombin (228). There may be excess antithromboplastin in acquired defects of coagulation [Beaumont (229)]. This appears with appreciable frequency in lupus erythematosus [Lee *et al.* (230)]. Whether lipide antithromboplastin plays a primary or a secondary role in hemophilia, its constant association with thromboplastin in the body suggests that it is important in the physiologic control of coagulation. The possibility should be borne in mind that the antihemophilic factors may function by neutralizing inhibitors.

Another type of antithromboplastin is that described by Schneider and by Thomas. This substance has been well characterized by Lanchantin & Ware (231): it reversibly inactivates tissue thromboplastin in the presence of calcium and is not increased in hemophilia [Chevallier *et al.* (222)]. Yet another antithromboplastin is that studied by Spaet & Garner (232): it inactivates the complex of platelet thromboplastin and prothrombin conversion factors. No calcium is required for its activity, which is unaffected by hemophilia.

Other inhibitors.—Wagner *et al.* (233) and also Jürgens (234) have described an inhibitor which progressively inactivates stable factor. Both papers conclude that the inhibitor differs from antithrombin, although there are some resemblances. Wagner *et al.* find the inhibitor to be inactivated by ether while Jürgens observes activation. It is unaffected by dicumarol and is normal in congenital deficiency of stable factor and in hemophilia. The inhibitors described by Kingsley (235) and by Shaefer *et al.* (236) may possibly be similar.

Spaet & Kinsell describe a circulating anticoagulant selectively active against human AHF (237). Richards & Spaet immunize rabbits against

human AHF (238). The antibody formed acts as an anticoagulant *in vitro* but does not increase the capacity of the serum to inactivate thromboplastin. Bonnin *et al.* report a case of lupus erythematosus with a circulating anticoagulant which appears to act primarily on prothrombin (239). Zucker observes that ethylene diamine tetraacetic acid inhibits the clotting of fibrinogen by thrombin (240); Triantaphyllopoulos *et al.* find it also inhibits labile factor (241). These inhibitory actions in addition to its decalcifying action may be partial explanation for the excellence of EDTA as an anticoagulant for bank blood, as was earlier reported by Proescher, whose important studies are continuing [Proescher & Nolan (242)].

Interactions and interrelationships.—In publications appearing over the period 1949 to 1952 the reviewer and coworkers described a reaction between stable factor, calcium, and thromboplastin of either tissue or platelet origin. This cothromboplastin reaction precedes the conversion of prothrombin to thrombin. In 1953 Flynn & Coon showed that three different complexes between tissue thromboplastin and prothrombin conversion factors could be isolated by high speed centrifugation (243). These complexes consisted of (*a*) thromboplastin plus stable factor (*b*) thromboplastin plus labile factor (*c*) thromboplastin plus stable factor plus labile factor. Neither of the first two complexes, each containing only one conversion factor, was active alone, but each would readily add the missing factor to form the third, complete complex. Calcium was required for stable factor to react but not for labile factor. The complete complex had the property of converting prothrombin to thrombin with great rapidity, without the addition of prothrombin conversion factors except the very small quantity of those factors combined in the complex. Mann & Hurn have confirmed in every particular the isolation of the three complexes described by Flynn & Coon, and have prepared three exactly analogous complexes with protein-free lipide thromboplastin (244). Biggs *et al.* (245) and also Hardisty (246) have confirmed the observation that both conversion factors react with tissue thromboplastin before prothrombin enters into the reaction. Using the centrifugation method of Flynn & Coon, Owren *et al.* confirmed the existence of the complex of thromboplastin and stable factor but at first did not regard the affinity of thromboplastin for labile factor as indicating an actual complex (247). Subsequently Seaman & Owren used the very strong affinity of labile factor for a phospholipide preparation (lipide thromboplastin) as a means of separating labile factor from plasma (248). In another paper they used the same material to remove prothrombin from plasma (249). About six years ago Mann *et al.* and Alexander, working independently, found that stable factor reacts with platelet thromboplastin in a manner exactly analogous to its reaction with tissue thromboplastin, calcium being required. Mann & Hurn confirm this finding with the centrifugation method (250). They regard the large amount of labile factor associated with platelets as part of a complex of thromboplastin plus labile factor. Hjort *et al.* conclude from a thorough study of the problem that the labile factor of the platelets is derived from the

plasma (251). Also in agreement with this view is the report of Deutsch that in congenital labile factor deficiency the platelets are deficient in this factor (252). Likewise Fiala & Roth find platelets to react with both conversion factors (253). Evidently thromboplastin of tissue protein, lipide, or platelet origin will form the identical three types of complexes with the prothrombin conversion factors. The complete complex containing both cothromboplastic factors and calcium has the property, even in concentrations in the range of μg per ml. of converting prothrombin to thrombin in a matter of seconds.

While there is excellent agreement regarding the reactions of thromboplastin with the two known cothromboplastic factors, the reactions of the antihemophilic factors present an unsolved problem of great complexity. Courageous attacks on this difficult problem are those of Biggs *et al.* (83) and Spurling & King (254). In these researches no complexes are isolated, as was accomplished by Flynn & Coon, and all must be inferred from reaction kinetics. Also, formation of thrombin is a serious problem in such experiments. In their initial paper Biggs *et al.* state flatly that thrombin did not form (84). Subsequently Macfarlane & Biggs (255) report small but demonstrable amounts of thrombin, as do Spurling & King. Isenschmid believes that the effect of such amounts of thrombin is merely an additive one in the final clotting mixture and hence it is easily corrected for (256). Biggs *et al.* (83) and Spurling & King agree with earlier workers that the initial presence of traces of thrombin may greatly accelerate subsequent reactions. Possibly this effect may be due to some intermediate complex of conversion factors rather than to thrombin; at any rate, it causes a problem in interpretation of these experiments where relatively large amounts of serum and serum products must be used.

Recognizing the complexity of the problem, Biggs *et al.* present several alternative schemes of intermediate reactions (83). A favored concept is that an intermediate substance called Product I forms from a reaction involving platelets, calcium, AHF, and PTC; this subsequently reacts with the labile and stable factors. Bergsagel & Hougie use the term Product I to indicate the product of a reaction between AHF, calcium, and some factor in serum believed to be PTC (257). Turning now also to the centrifugation method of Flynn & Coon (243), Bergsagel & Hougie find that Product I reacts with platelet granules to form a sedimentable coagulant (257). Bergsagel observes this intermediate product to produce clumping and viscous metamorphosis of platelets (258). Hougie notes an activation effect of plasma on platelets in the absence of calcium (259). Bergsagel reports another intermediate reaction, between calcium and PTC (260). Spurling & King conclude that the basic intermediate reaction involves PTC, platelets, and calcium, that AHF accelerates this reaction (254). It is of course apparent that all of the foregoing studies have attempted to deal with only two antihemophilic factors, AHF and PTC, not the six that have been claimed to exist, thus far.

Pavlovsky, who first concluded over ten years ago that there are different types of hemophilia, has brought forward other findings which are not yet

assimilated into current concepts of the disease: in the course of their lives hemophilics may change not only in severity but in type (261). Pavlovsky and co-workers have recently published more data from their vast experience bearing on the question of the nature of hemophilia (262). They think in terms of two main forms of hemophilia, designated as A and B, but with a number of individuals difficult to classify because of partial lack of either or both factors in varying proportions; and because of the presence of inhibitors. Along the same lines, Fantl & Sawers find that closely related hemophilics may be of different types (263). Already, several cases of combined deficiencies of antihemophilic and cothromboplastic factors have been reported: AHF plus labile factor [Oeri *et al.* (264)]; PTC plus stable factor [Bell & Alton (265), Deutsch *et al.* (266)]; AHF plus PTC [Verstraete & Vandenbrouke (267)]; labile factor plus stable factor [Van Creveld & Veder (268)]. These clearly suggest that genetic or other interrelationships exist as none of these conditions are common.

In the studies of Mann & Hurn it was found that the two types of incomplete complexes of thromboplastin did not supplement each other on mixing (244). It was necessary for both of the cothromboplastic factors to be combined together on the same particle of thromboplastin. The inference is that these two protein molecules, relatively small compared to the particle of thromboplastin, are close together at a specific reaction site for the conversion of prothrombin to thrombin. The reviewer admits being personally attracted to the idea that this may be all that is necessary. According to such a scheme of things the antihemophilic factors would be thought of as molecules very similar to the prothrombin conversion factors, and subject to genetic modifications affecting differently their reactivity to platelet thromboplastin. Reasoning by analogy with the blood groups and hemoglobins, such genetic modifications could be numerous. It is not necessary for all types of agglutinins to be present in order for erythrocytes to be agglutinated. Accordingly the antihemophilic factors would be thought of as functional alternates of the prothrombin conversion factors. No apology is offered for expressing the hope that it is not necessary to think of eight or more obligatory participants in a complex scheme of serial reactions. It would be as difficult for eight molecules to get together on one point as for eight coagulationists.

LITERATURE CITED

1. Alexander, B., *New Engl. J. Med.*, **252,** 432–42, 484–94, 526–35 (1955)
2. Seegers, W. H., *Advances in Enzymol.*, **16,** 23–203 (1955)
3. Koller, F., *Acta Haematol.*, **12,** 342–68 (1954); **13,** 307–36; **14,** 100–44 (1955); **15,** 46–78 (1956)
4. Tocantins, L. M., *The Coagulation of Blood, Methods of Study* (Grune & Stratton, New York, N. Y., 240 pp., 1955)
5. Deutsch, E., *Blutgerinnungsfaktoren* (Franz Deuticke, Wien, Vienna, Austria, 298 pp., 1955)
6. Erkelens, A. D., *De Plaats der Thrombocyten in het Stollingsproces* (Boerman en Zoon, Rotterdam, The Netherlands, 174 pp., 1956)
7. Ferguson, J. H., *Am. J. Physiol.*, **108,** 670–82 (1934)
8. Bloom, G., *Z. Zellforsch. u mikroskop Anat.*, **40,** 222–27 (1954)
9. Bloom, G., *Z. Zellforsch. u mikroskop Anat.*, **42,** 365–85 (1955)
10. D'Antuono, G., and Pieragnoli, E., *Giorn. clin. med.*, **36,** 788–811 (1955)
11. De Robertis, E., *Blood*, **10,** 528–33 (1955)
12. Braunsteiner, H., Fellinger, K., and Pakesch, F., *Blood*, **9,** 595–601 (1954)
13. Fieschi, A., *Athena*, **20,** 385–89 (1954)
14. Aleksandrowicz, J., Blicharski, J., and Feltynowski, F., *Le Sang*, **25,** 67–70 (1954)
15. Fonio, A., *Ergeb. der inn. Med. und Kinderheilk.*, **4,** 1–51 (1953)
16. Bessis, M., and Tabuis, J., *Rev. Hematol.*, **10,** 753–71 (1955)
17. Jürgens, R., *Wien. klin. Wochschr.*, **66,** 850–52 (1954)
18. Deutsch, E., *Rev. Hématol.*, **9,** 483–88 (1954)
19. Schneider, C. L., Claxton, E. B., Hughes, C. H., and Johnson, S. A., *Am. J. Physiol.*, **179,** 236–42 (1954)
20. Alkjaersig, N., Takeshi, A., and Seegers, W. H., *Am. J. Physiol.*, **181,** 304–8 (1955)
21. Stafanini, M., and Campbell, E. W., *Rev. Hématol.*, **9,** 576–85 (1954)
22. Baserga, A., *Le Sang*, **25,** 742–51 (1954)
23. De Nicola, P., *Rev. Hématol.*, **9,** 536–42 (1954)
24. Larrieu, M. J., Caen, J., and Bernard, J., *Rev. Hématol.*, **10,** 719–24 (1955)
25. O'Brien, J. R., *Brit. J. Haematol.*, **1,** 223–28 (1955)
26. Van Creveld, S., and Paulssen, M. M. P., *Ann. Paediat.*, **181,** 193–200 (1953)
27. Van Creveld, S., and Veder, H. A., *Ann. Paediat.*, **185,** 236–41 (1955)
28. De Vries, A., Shafrir, E., Efrati, P., and Shamir, Z., *Blood*, **8,** 1000–7 (1953)
29. Soulier, J. P., Larrieu, M. J., and Wartelle, O., *Acta Haematol.*, **14,** 160–176 (1955)
30. Neely, R. A., Carson, N. A. J., and Fisher, O. D., *Brit. J. Haematol.*, **1,** 234–40 (1955)
31. Braunsteiner, H., *Wien. Z. inn. Med.*, **36,** 421–71 (1955)
32. De Nicola, P., and Rosti, P., *Experientia*, **10,** 24–25 (1954)
33. Savitsky, J. P., and Werman, R., *Am. J. Clin. Pathol.*, **24,** 161–65 (1954)
34. Bounameaux, Y., *Rev. belge pathol., et med. exp.*, **24,** 149–53 (1955)
35. Lawkowicz, W., Czerski, P., and Porembinska, H., *Rev. belge pathol., et med. exp.*, **24,** 524–23 (1955)
36. Cronkite, E. P., Jacobs, G. J., and Schork, P. K., *Radiation Research*, **2,** 439–46 (1955)

37. Gregoire, C., *Arch. intern. physiol.*, **63**, 246–48 (1955)
38. Gurevitch, J., and Nelken, D., *J. Lab. Clin. Med.*, **44**, 562–70 (1954)
39. Moureau, P., and Andre, A., *Nature*, **174**, 88 (1954)
40. Koppel, J. L., and Olwin, J. H., *Proc. Soc. Exptl. Biol. Med.*, **86**, 641–45 (1954)
41. Stefanini, M., and Murphy, I. S., *J. Clin. Invest.*, **35**, 355–61 (1956)
42. Salvidio, E., *Acta Haematol.*, **11**, 301–08 (1954)
43. De Robertis, E., Paseyro, P., and Reissig, M., *Blood*, **8**, 587–97 (1953)
44. Bounameaux, Y., *Arch. intern. physiol.*, **63**, 243–45 (1955)
45. Desforges, J. F., and Bigelow, F. S., *Blood*, **9**, 153–62 (1954)
46. Zucker, M. B., and Borrelli, J., *J. Appl. Physiol.*, **7**, 425–42 (1955)
47. Bounameaux, Y., and Lecomte, J., *Arch. intern. physiol.*, **62**, 543–44 (1954)
48. Fenichel, R. L., and Seegers, W. H., *Am. J. Physiol.*, **181**, 19–20 (1955)
49. Harrington, W. J., *Le Sang*, **25**, 712–25 (1954)
50. Stefanini, M., Plitman, G. I., Damashek, W., Chatterjea, J. B., and Mednicoff, I. B., *J. Lab. Clin. Med.*, **42**, 723–38 (1953)
51. Capaldo, A., and Del Buono, G., *Riv. biol.*, **46**, 253–59 (1954)
52. Hecht, E., *Biochem. Z.*, **326**, 325–42 (1955)
53. Stein, H. B., and Abrahams, O., *S. African J. Med. Sci.*, **19**, 79–96 (1954)
54. Phillips, G. E., and Lenahan, J. G., *J. Lab. Clin. Med.*, **46**, 713–19 (1955)
55. Walter, O., and Schmutzler, R., *Z. ges. inn. Med. u ihre Grenzgebiete*, **9**, 592–97 (1954)
56. Izarn, P., Hussey, C. V., and Quick, A. J., *Proc. Soc. Exptl. Biol. Med.*, **91**, 193–95 (1956)
57. Kok, K., *Acta Physiol. et Pharmacol. Neerl.*, **4**, 51–81 (1955)
58. Copley, A. L., *Rev. belge pathol. et med. exp.*, **24**, 128–35 (1955)
59. Gollub, S., *J. Appl. Physiol.*, **7**, 409–12 (1955)
60. Sapuppo, C., *Riv. biol.*, **46**, 441–49 (1954)
61. Von Kaulla, K. N., *Proc. Soc. Exptl. Biol. Med.*, **91**, 543–45 (1956)
62. Kaliampetsos, G., *Klin. Wochschr.*, **34**, 438–42 (1956)
63. Shinowara, G. Y., Waite, J. H., and Saleeby, R. G., *Proc. Soc. Exptl. Biol. Med.*, **83**, 423–26 (1953)
64. Schneider, C. L., *Obstet. and Gynecol.*, **4**, 273–94 (1954)
65. Georgatsos, J. G., Hussey, C. V., and Quick, A. J., *Am. J. Physiol.*, **180**, 30–34 (1955)
66. Ottaviani, P., Dettori, A., and Manai, G., *Arch. sci. med.*, **98**, 1–16 (1954)
67. Fogelman, M. J., Robins, K. I., Hennington, R., and Stapp, W. F., *Surgical Forum 38th Congress Am. College of Surgeons*, 467–74 (1953)
68. Niewlarowski, S., and Panasewicz, J., *Acta Physiol. Polon.*, **5**, 191–205 (1954)
69. McKay, D. G., Hardaway, R. M., Wahle, G. H., Edelstein, R., and Tartock, D. E., *Am. J. Surg.*, **89**, 583–92 (1955)
70. De Vries, S. I., Kettenborg, H. K., and Van der Pol, E. T., *Rev. belge pathol. et med. exp.*, **24**, 154–58 (1955)
71. Leupold, R., *Schweiz. med. Wochschr.*, **85**, 911 (1955)
72. Duckert, F., *Schweiz. med. Wochschr.*, **85**, 912 (1955)
73. Bell, W. N., and Alton, H. G., *Nature*, **174**, 880–81 (1954)
74. Newlands, M. J., and Wild, F., *Nature*, **176**, 885–86 (1955)
75. Poole, J. C. F., *Brit. J. Haematol.*, **1**, 229–33 (1955)
76. Robinson, D. S., *Quart. J. Exptl. Physiol.*, **40**, 112–26 (1955)

77. O'Brien, J. R., *Lancet*, **II**, 690–93 (1955)
78. Manning, P. R., and Walford, R. L., *Am. J. Med. Sci.*, **228**, 652–55 (1954)
79. Dick, F. W., Jackson, D. P., and Conley, C. L., *J. Clin. Invest.*, **33**, 1423–33 (1954)
80. Fantl, P., and Hayes, R. A., *Nature*, **172**, 303–4 (1953)
81. Feissly, R., *Rev. belge pathol. et med. exp.*, **24**, 159–66 (1955)
82. Rapaport, S. I., Aas, K., and Owren, P. A., *J. Clin. Invest.*, **34**, 9–19 (1955)
83. Biggs, R., Douglas, A. S., and Macfarlane, R. G., *J. Physiol.* (*London*), **122**, 538–53 (1953)
84. Biggs, R., Douglas, A. S., and Macfarlane, R. G., *J. Physiol.* (*London*), **119**, 89–101 (1953)
85. Alagille, D., *Rev. intern. hépatol.*, **4**, 1–183 (1954)
86. Owen, C. A., Jr., and Cooper, T., *Arch. Internal Med.*, **95**, 194–201 (1955)
87. Vetter, H., and Vinagger, H., *Blood*, **9**, 163–72 (1954)
88. Alkjaersig, N., and Seegers, W. H., *Am. J. Physiol.*, **182**, 347–50 (1955)
89. Cox, F. W., Lanchantin, G. W., and Ware, A. G., *J. Clin. Invest.*, **35**, 106–13 (1956)
90. Barkham, P., *S. African J. Med. Sci.*, **19**, 141–46 (1954)
91. Douglas, A. S., *Clin. Sci.*, **14**, 601–13 (1955)
92. Jürgens, J., *Arch. intern., pharmacodynamie*, **105**, 1–32 (1956)
93. Beaumont, J. L., and Gele, P., *Le Sang*, **24**, 748–61 (1953)
94. Walker, W., and Hunter, R. B., *J. Clin. Pathol.*, **7**, 249–51 (1954)
95. Glueck, H. I., Sherry, S., and Troll, W., *Proc. Soc. Exptl. Biol. Med.*, **87**, 646–50 (1954)
96. Long, L. A., Letandre, P., and Colpron, G., *Acta Haematol.*, **13**, 242–49 (1955)
97. Witte, S., and Dirnberger, P., *Klin. Wochschr.*, **31**, 781–87 (1953)
98. Passaro, G., *Boll. soc. ital. biol. sper.*, **31**, 129–32 (1955)
99. Alexander, B., Meyers, L., Kenny, J., Goldstein, R., Gurevitch, V., and Grinspoon, L., *New Engl. J. Med.*, **254**, 358–63 (1956)
100. Hill, J. M., Speer, R. J., Roberts, A., and Maloney, M., *J. Lab. Clin. Med.*, **45**, 308–12 (1955)
101. Dam, H., and Sondergaard, E., *Acta Physiol. Scand.*, **31**, 376–83 (1954)
102. Quick, A. J., Pisciotta, A. V., and Hussey, C. V., *Arch. Internal Med.*, **95**, 1–14 (1955)
103. Seegers, W. H., Alkjaersig, N., and Johnson, S. A., *Am. J. Clin. Pathol.*, **25**, 983–87 (1955)
104. Lewis, J., and Ferguson, J. H., *J. Clin. Invest.*, **32**, 915–21 (1953)
105. De Nicola, P., *Haematologica*, **38**, 903–25 (1954)
106. Deutsch, E., and Schaden, W., *Biochem. Z.*, **324**, 266–79 (1953)
107. Witte, S., and Dirnberger, P., *Acta Haematol.*, **9**, 380–8 (1953)
108. Owen, C. A., Jr., and McKenzie, B. F., *J. Appl. Physiol.*, **6**, 696–700 (1954)
109. Brinkhous, K. M., *Le Sang*, **25**, 738–41 (1954)
110. Brinkhous, K. M., and Graham, J. B., *Blood*, **9**, 254–57 (1954)
111. Langdell, R. D., Wagner, R. H., and Brinkhous, K. M., *Proc. Soc. Exptl. Biol. Med.*, **88**, 212–15 (1955)
112. Graham, J. B., McLendon, W. W., and Brinkhous, K. M., *Am. J. Med. Sci.*, **225**, 46–53 (1953)
113. Sjølin, K., *Acta Pathol. et Microbiol. Scand.*, **35**, 512–22 (1954)

114. Boivin, J. M., *Arch. maladies coeur et oaisseaux*, **47**, 351–54 (1954)
115. Pool, J. G., and Spaet, T. H., *Proc. Soc. Exptl. Biol. Med.*, **87**, 54–57 (1954)
116. O'Brien, J. G., *J. Clin. Pathol.*, **7**, 22–25 (1954)
117. Van Creveld, S., Hoorweg, P. G., Den Ottolander, G. J. H., and Veder, H. A., Ned. Tijdschr. Geneesk., **99**: 2269–75 (1955)
118. Spaet, T. H., and Kinsell, B. G., *Proc. Soc. Exptl. Biol. Med.*, **84**, 314–17 (1953)
119. Bidwell, E., *Brit. J. Haematol.*, **1**, 386–89 (1955)
120. Lorand, L., and Laki, K., *Biochim et Biophys. Acta*, **13**, 448–49 (1954)
121. Murray, M., Johnson, S. A., and Seegers, W. H., *Am. J. Physiol.*, **178**, 10–16 (1954)
122. Emmenegger, H., and Lüscher, E., *Helv. Physiol. et Pharmacol. Acta*, **12**, C13–15 (1954)
123. Aggeler, P. M., White, S. G., and Spaet, T. H., *Blood*, **9**, 246–53 (1954)
124. Aggeler, P. M., Spaet, T. H., and Emery, B. E., *Science*, **119**, 806–7 (1954)
125. Soulier, J. P., and Larrieu, M. J., *New Engl. J. Med.*, **249**, 547–53 (1953)
126. Fantl, P., and Sawers, R. J., *Australasian Ann. Med.*, **3**, 245–62 (1954)
127. Frick, P. G., *J. Lab. Clin. Med.*, **43**, 860–66 (1954)
128. Rosenthal, M. C., *Am. J. Clin. Pathol.*, **24**, 910–17 (1954)
129. Rosenthal, R. L., *Am. J. Med.*, **17**, 57–69 (1954)
130. Verstraete, M., *De Vorming van Plasma-Thromboplastine* (Arscia, Brussels, Belgium, 370 pp., 1955)
131. Camera, A., *Boll. soc. ital. biol. sper.*, **29**, 1824–27 (1953)
132. Sise, H. S., Kimball, D. M., and Adamis, D., *Proc. Soc. Exptl. Biol. Med.*, **89**, 81–83 (1955)
133. Naeye, R. L., *Proc. Soc. Exptl. Biol. Med.*, **91**, 101–4 (1956)
134. Johnson, S. A., and Seegers, W. H., *Circulation Research*, **4**, 182–86 (1956)
135. Rosenthal, R. L., *J. Lab. Clin. Med.*, **45**, 123–29 (1955)
136. Ramot, B., Angelopoulos, B., and Singer, K., *Arch. Internal Med.*, **95**, 705–12 (1955)
137. Spaet, T. H., Aggeler, P. M., and Kinsell, B. E., *J. Clin. Invest.*, **33**, 1095–1102 (1954)
138. Ratnoff, O. D., and Colopy, J. E., *J. Clin. Invest.*, **34**, 602–13 (1955)
139. Frick, P. G., and Hagen, P. S., *J. Lab. Clin. Med.*, **47**, 592–601 (1956)
140. Bell, W. N., Tomlin, S. C., and Archer, R. K., *J. Comp. Pathol. and Therap.*, **65**, 255–61 (1955)
141. Duckert, F., Flückiger, P., Matter, M., and Koller, F., *Proc. Soc. Exptl. Biol. Med.*, **90**, 17–22 (1955)
142. Walker, W., and Hunter, R. B., *Nature*, **173**, 1192 (1954)
143. Beller, F. K., and Mammen, E., *Klin. Wochschr.*, **33**, 155–56 (1955)
144. Fiehrer, A., Renault, H., Lemonnier, A., and Funel, P., *Le Sang*, **26**, 598–602 (1955)
145. Lasch, H. G., and Roka, L., *Hoppe-Seyler's Z. physiol. Chem.*, **294**, 30–35 (1953)
146. Lasch, H. G., and Roka, L., *Klin. Wochschr.*, **32**, 460–64 (1954)
147. Duckert, F., Koller, F., and Matter, M., *Proc. Soc. Exptl. Biol. Med.*, **82**, 259–61 (1953)
148. Biggs, R., and Douglas, A. S., *J. Clin. Pathol.*, **6**, 15–22 (1953)
149. Alkjaersig, N., and Seegers, W. H., *Am. J. Physiol.*, **183**, 111–13 (1955)

150. Witte, S., and Dirnberger, P., *Klin. Wochschr.*, **31**, 936–39 (1953)
151. Forel, M. M., and Koller, F., *Münch. med. Wochschr.*, **95**, 433–37, (1953)
152. Hunter, R. B., and Walker, W., *Thrombosis and Embolism First International Conference*, pp. 116–120 (Benno Schwabe, Basel, Switzerland, 1955)
153. Jaques, L. B., *Rev. Hematol.*, **10**, 379–84 (1955)
154. Jaques, L. B., Millar, G. J., and Spinks, J. W. T., *Schweiz med. Wochschr.*, **84**, 792–96 (1954)
155. Carter, J. R., and Warner, E. D., *Am. J. Physiol.*, **184**, 195–201 (1956)
156. Ray, G., Ganguli, N. C., and Roy, S., *Nature*, **172**, 809–10 (1953)
157. Laki, K., Kominz, D. R., Symonds, P., Lorand, L., and Seegers, W. H., *Arch. Biochem.*, **49**, 276–82 (1954)
158. Milstone, J. H., *J. Gen. Physiol.*, **38**, 743–55 (1955)
159. Seegers, W. H., and Alkjaersig, N., *Arch. Biochem.*, **61**, 1–19 (1956)
160. Lorand, L., Alkjaersig, N., and Seegers, W. H., *Arch. Biochem.*, **45**, 312–18 (1953)
161. Miller, K. D., and Seegers, W. H., *Arch. Biochem.*, **60**, 398–401 (1956)
162. Alkjaersig, N., Takeshi, A., Johnson, S. A., and Seegers, W. H., *Am. J. Physiol.*, **182**, 443–46 (1955)
163. Seegers, W. H., and Alkjaersig, N., *Circulation Research*, **3**, 514–18 (1955)
164. Seegers, W. H., and Johnson, S. A., *Am. J. Physiol.*, **184**, 259–64 (1956)
165. Seegers, W. H., Alkjaersig, N., and Johnson, S. A., *Am. J. Physiol.*, **181**, 589–94 (1955)
166. Milstone, J. H., *J. Gen. Physiol.*, **38**, 757–69 (1955)
167. Alkjaersig, N., Deutsch, E., and Seegers, W. H., *Am. J. Physiol.*, **180**, 367–70 (1955)
168. Kleinfeld, G., and Habif, D. V., *Proc. Soc. Exptl. Biol. Med.*, **84**, 432–37 (1953)
169. Sherry, S., Troll, W., and Glueck, H. I., *Physiol. Rev.*, **34**, 736–41 (1954)
170. Bagby, D., and Szara, S., *Acta Physiol. (Budapesti)*, **7**, 179–81 (1955)
171. Szara, S., and Bagby, D., *Acta Physiol. (Budapesti)*, **4**, 229–33 (1953)
172. Bailey, K., and Bettelheim, F. R., *Biochim. et Biophys. Acta*, **18**, 495–503 (1955)
173. Bettelheim, F. R., *Biochim. et Biophys. Acta*, **19**, 121–30 (1956)
174. De Vries, A., Shafrir, E., Biezunski, N., Ginsburg, J., and Katchalski, E., *Rev. belge pathol. et med. exp.*, **24**, 112–16 (1955)
175. Fanconi, G., *Acta Paediat.*, **43**, 275–84 (1954)
176. Ratnoff, O. D., and Potts, A. M., *J. Clin. Invest.*, **33**, 206–10 (1954)
177. Craddock, C. G., Adams, W. S., and Figueroa, W. G., *J. Lab. Clin. Med.*, **42**, 847–59 (1953)
178. Frick, P. G., *Am. J. Clin. Pathol.*, **25**, 1263–73 (1955)
179. Gehmacher, K., Herold, G., and Reimer, E. E., *Wien. Z. inn. Med.*, **35**, 245–50 (1954)
180. Ratnoff, O. D., *J. Clin. Invest.*, **33**, 1175–81 (1954)
181. Kekwick, R. A., Mackay, M. E., Nance, M. H., and Record, B. R., *Biochem. J. (London)*, **60**, 671–83 (1955)
182. Sheppard, E., and Wright, I. S., *Arch. Biochem.*, **52**, 414–58 (1954)
183. Rieser, P., *Proc. Soc. Exptl. Biol. Med.*, **91**, 654–57 (1956)
184. Burstein, M., and Guinand, A., *J. Physiol. (Paris)*, **46**, 799–807 (1954)
185. Burstein, M., and Guinand, A., *Rev. Hematol.*, **9**, 231–42; 650–57 (1954)

186. Burstein, M., and Guinand, A., *Le Sang*, **25**, 919–25 (1954)
187. Burstein, M,. Lewi, S., and Walter, P., *Le Sang*, **25**, 102–7 (1954)
188. Greene, R. W., *J. Clin. Invest.*, **34**, 417–27 (1955)
189. Ingram, G. I. C., *J. Clin. Pathol.*, **8**, 318–23 (1955)
190. Lyons, R. N., *Australian J. Exptl. Biol. Med. Sci.*, **32**, 113–21 (1954)
191. Guest, M. M., *J. Clin. Invest.*, **33**, 1553–59 (1954)
192. Sherry, S., *J. Clin. Invest.*, **33**, 1054–63 (1954)
193. Ratnoff, O. D., *J. Clin. Invest.*, **32**, 473–79 (1953)
194. Kwaan, H. C., McFadyean, A. J. S., and Cook, J., *Lancet*, **I**, 132–36 (1956)
195. Dolaz, E. J., Dolehide, R. A., and Friedman, I. A., *Illinois Med. J.*, **107**, 142–44 (1955)
196. Malagamba, G., *Arch. "E. Maragliano" patol. e clin.*, **8**, 801–8 (1953)
197. Obersteg, J. I., *Deut., Z. ges. gerichtl. Med.*, **43**, 177–216 (1954)
198. Fearnley, G. R., and Lackner, R., *Brit. J. Haematol.*, **1**, 189–98 (1955)
199. Seegers, W. H., Johnson, J. F., and Fell, C., *Am. J. Physiol.*, **176**, 97–103 (1954)
200. Fell, C., Ivanovic, H., Johnson, S. A., and Seegers, W. H., *Proc. Soc. Exptl. Biol. Med.*, **85**, 199–202 (1954)
201. Quick, A. J., *Le Sang*, **25**, 726–37 (1954)
202. Wenckert, A., *Acta Haematol.*, **14**, 22–34 (1955)
203. Monkhouse, F. C., France, E. S., and Seegers, W. H., *Circulation Research*, **3**, 397–402 (1955)
204. Fitzgerald, M. A., and Waugh, D. F., *Arch. Biochem.*, **58**, 431–52 (1955)
205. Waugh, D. F., and Fitzgerald, M. A., *Am. J. Physiol.*, **184**, 627–39 (1956)
206. Burstein, M., *Arch. intern. pharmacodynamie*, **101**, 285–308 (1955)
207. Burstein, M., and Guinand, A., *Arch. intern. pharmacodynamie*, **104**, 435–44 (1956)
208. Chevallier, P., Fiehrer, A., Bilski-Pasquier, G., Mathieu, H., Samama, E., and Funel, P., *Le Sang*, **26**, 533–37 (1955)
209. Jürgens, J., *Deut. Arch. Klin. Med.*, **200**, 67–85 (1953)
210. Brambel, C. E., Corwin, A. H., and Capone, V. A., *Am. J. Med. Sci.*, **230**, 276–92 (1955)
211. Douglas, A. S., *J. Clin. Invest.*, **35**, 533–36 (1956)
212. Freeman, L., Engelberg, H., and Dudley, A., *Am. J. Clin. Pathol.*, **24**, 599–606 (1954)
213. Engelberg, H., Dudley, A., and Freeman, L., *J. Lab. Clin. Med.*, **46**, 653–56 (1955)
214. Nilson, J. M., and Wenckert, A., *Demonstration of a Heparin-Like Anticoagulant in Normal Blood* (Berlingska Boktryckeriet, Lund, 146 pp., 1954)
215. Wenckert, A., and Nilson, J. M., *Thromboplastin and Russell Viper Venom*, (Berlingska Boktryckeriet, Lund, Sweden 97 pp., 1955)
216. Bragdon, J. H., and Havel, R. J., *Science*, **120**, 113–14 (1954)
217. Terzioglu, M., and Ozer, F., *Arch. intern. physiol.*, **64**, 1–14 (1956)
218. Raths, P., and Perlick, E., *Z. Biol.*, **106**, 305–18 (1953)
219. Perlick, E., *Arch. klin. Chir.*, **279**, 799–802 (1954)
220. Smith, D. E., Lewis, Y. S., and Svihla, G., *Experientia*, **10**, 218 (1954)
221. Tocantins, L. M., *Blood*, **9**, 281–85 (1954)
222. Chevallier, P., Fiehrer, A., Bilski-Pasquier, G., and Samama, A., *Le Sang*, **26**, 362–80 (1955)

223. Johnson, S. A., *Am. J. Clin. Pathol.*, **23,** 875–80 (1953)
224. Johnson, S. A., Deutsch, E., and Seegers, W. H., *Am. J. Physiol.*, **179,** 149–53 (1954)
225. Johnson, S. A., and Seegers, W. H., *Rev. Hematol.*, **9,** 529–35 (1954)
226. Chevallier, P., Fiehrer, A., and Samama, M., *Le Sang*, **26,** 528–32 (1955)
227. Rapaport, S. I., Aas, K., and Owren, P. A., *J. Lab. Clin. Med.*, **44,** 364–73 (1954)
228. Seegers, W. H., Johnson, S. A., Fell, C., and Alkjaersig, N., *Am. J. Physiol.*, **178,** 1–9 (1954)
229. Beaumont, J. L., *Le Sang*, **25,** 1–15 (1954)
230. Lee, S. L., Sanders, M., and Kahny, H. M., *J. Clin. Invest.*, **34,** 1814–23 (1955)
231. Lanchantin, G. F., and Ware, A. G., *J. Clin. Invest.*, **32,** 381–89 (1953)
232. Spaet, T. H., and Garner, E. S., *J. Clin. Invest.*, **34,** 1807–13 (1955)
233. Wagner, R. H., Brannan, W. M., and Brinkhous, K. M., *Proc. Soc. Exptl. Biol. Med.*, **89,** 266–70 (1955)
234. Jürgens, J., *Acta Haematol.*, **14,** 57–62 (1955)
235. Kingsley, C. S., *Nature*, **173,** 723–4 (1954)
236. Schaefer, E. H., Therriault, D. G., and Jensen, H., *J. Appl. Physiol.*, **8,** 300–4 (1955)
237. Spaet, T. H., and Kinsell, B. G., *Stanford Med. Bull.*, **12,** 246–56 (1954)
238. Richards, M. D., and Spaet, T. H., *Blood*, **11,** 473–83 (1956)
239. Bonnin, J. A., Cohen, A. K., and Hicks, N. D., *Brit. J. Haematol.*, **2,** 168–79 (1956)
240. Zucker, M. B., *Am. J. Clin. Pathol.*, **24,** 39–41 (1954)
241. Triantaphyllopoulos, D. C., Quick, A. J., and Greenwalt, T. J., *Blood*, **10,** 534–44 (1955)
242. Proescher, F., and Nolan, J., *Calif. Med.*, **81,** 221–25 (1954)
243. Flynn, J. E., and Coon, R. W., *Am. J. Physiol.*, **175,** 289–95 (1953)
244. Mann, F. D., and Hurn, M., *Am. J. Physiol.*, **182,** 319–24 (1955)
245. Biggs, R., Douglas, A. S., and Macfarlane, R. G., *J. Physiol. (London)*, **122,** 554–99 (1953)
246. Hardisty, R. M., *Brit. J. Haematol.*, **1,** 323–32 (1955)
247. Owren, P. A., Rapaport, S. I., Hjort, P., and Aas, K., *Le Sang*, **25,** 752–65 (1954)
248. Seaman, A. J., and Owren, P. A., *J. Clin. Invest.*, **35,** 145–49 (1956)
249. Seaman, A. J., and Owren, P. A., *J. Clin. Invest.*, **35,** 371–73 (1956)
250. Mann, F. D., and Hurn, M., *Am. J. Physiol.*, **175,** 65–68 (1953)
251. Hjort, P., Rapaport, S. I., and Owren, P. A., *Blood*, **10,** 1139–50 (1955)
252. Deutsch, E., *Wien. Z. inn. Med.*, **36,** 355–57 (1955)
253. Fiala, S., and Roth, K., *Arch. intern. physiol.*, **61,** 205–23 (1953)
254. Spurling, C. L., and King, P. D., *J. Lab. Clin. Med.*, **44,** 336–48 (1954)
255. Macfarlane, R. G., and Biggs, R., *Le Sang*, **26,** 181–90 (1955)
256. Isenschmid, H., *Acta Haematol.*, **13,** 177–89 (1955)
257. Bergsagel, D. E., and Hougie, C., *Brit. J. Haematol.*, **2,** 113–29 (1956)
258. Bergsagel, D. E., *Brit. H. Jaematol.*, **2,** 130–38 (1956)
259. Hougie, C., *Brit. J. Haematol.*, **1,** 213–22 (1955)
260. Bergsagel, D. E., *Brit. J. Haematol.*, **1,** 199–212 (1955)
261. Pavlovsky, A., *Blood*, **9,** 291–93 (1954)

262. Pavlovsky, A., Bergna, L. J., and Canaveri, A. A. M., *Le Sang*, **26**, 162–81 (1955)
263. Fantl, P., and Sawers, R. J., *Brit. J. Haematol.*, **2**, 102–5 (1956)
264. Oeri, J., Matter, M., Isenschmid, H., Hauser, F., and Koller, F., *Bibliotheca Paediat.*, **58**, 575–88 (1954)
265. Bell, W. N., and Alton, H. G., *Brit. Med. J.*, **I**, 330–31 (1955)
266. Deutsch, E., Kundratitz, K., Frischauf, H., Jurka, J., and Schaden, W., *Arch. Kinderheilk.*, **148**, 115–134 (1954)
267. Verstraete, M., and Vandenbrouke, J., *Brit. Med. J.*, **II**, 1533–35 (1955)
268. Van Creveld, S., and Veder, H. A., *Ned. Tijdschr. Geneesk.*, **100**, 407–11 (1956)

BLOOD VOLUME AND ITS REGULATION[1]

By Ellen Brown, James Hopper, Jr., and Reidar Wennesland
Department of Medicine, University of California School of Medicine, San Francisco, California

Pertinent reviews on blood volume include those of Berson (1) and of Berlin, and co-workers (2). Grant & Root (3) have laid the background for the rapidly growing literature on the humoral factors that influence red cell production. Sjöstrand (4, 5) and Gauer (6) have discussed regulatory mechanisms, the former chiefly from the point of view of the distribution of the blood, and the latter with respect to the venomotor system and volume receptors.

We will give particular attention to the measurement of the entire blood volume and the mechanisms controlling it. Limitations of space require that we avoid detailed consideration of the distribution of the blood and limit discussion of pathologic states. After first discussing methods and normal values, we will review descriptions of the blood volume during stress and in disease and then summarize current concepts concerning regulatory mechanisms.

METHODS

Methods for determining the total volume of circulating red cells (red cell volume) have been much improved. At present, the use of radioactive chromium [Cr^{51}, Sterling & Gray (7)] seems the most reliable and simple [Eisenberg (8); (9, 10); Abajian (11); Donohue *et al.* (12); Gunton & Paul (13); Mollison & Veall (14); Huff & Feller (15); Walser *et al.* (16)]. Modifications described consist mostly in a reduction of the injected amount of labeled cells, made possible by advances in counting equipment and the availability of Cr^{51} of higher specific activity. Knowledge has been gained about the Cr^{51}-red cell bond, the viability of Cr^{51}-labeled cells, and the leakage and lack of reutilization of eluted Cr^{51} through studies of Necheles, Weinstein & LeRoy (17) and Cooper & Owen (18). Erythrocytes labeled *in vivo* take up only 10 to 12 per cent of the Cr^{51} but give a decay curve similar to that obtained by labeling *in vitro* [Sutherland & McCall (19)]. Repeated washing of the erythrocytes seems of little consequence, as shown by Hughes Jones & Mollison (20). The lungs and the spleen are the seats of early sequestration of Cr^{51}-labeled cells, not great enough to be of practical importance [Wennesland, *et al.* (21)]. Washing the red cells can be obviated by using ascorbic acid, which reduces the chromate remaining in the plasma [Read (22)]. Because exposure to plasma alone renders a certain amount of Cr^{51} inactive for red cell labeling (18, 19), the ascorbic acid may be unnecessary.

Other isotopes have been used more rarely, i.e., Fe^{55} and Fe^{59}, N^{15}, C^{14}

[1] This report will deal largely with articles that have appeared during the four years between June 30, 1952 and July 1, 1956.

[for references see Reeve (23)], "thorium B" [Hevesy & Nylin (24)], and K^{42} (25) [Yalow & Berson (26)]. Next to Cr^{51}, only P^{32} has been widely employed (23) [Chaplin *et al.* (27, 28)]. Nickerson, Sear & Reeve (29) found good correspondence in simultaneous measurements with Fe^{55} and P^{32}. P^{32} has the disadvantage of a rather rapid leakage from the cells (23, 27). P^{32} in diisopropylfluorophosphonate has been suggested for studies of red cell volume because it is irreversibly bound to the cells and plasma proteins [Cohen & Warringa (30)]. Carbon monoxide as a labeling agent has been replaced more and more by isotopes. The CO method devised by Sjöstrand (31), which has been used extensively in Sweden, depends upon analysis of the alveolar air after inhalation of small amounts of CO. Results based on this method have been reviewed (4, 5). Unfortunately, the fate of CO in the body is not completely known. It may be slowly metabolized (32), small amounts may be formed by the decomposition of hemoglobin (33), and it is distributed to extravascular pigment stores, particularly myoglobin (21).

Measurement of plasma volume remains a controversial subject, mainly because the blood volume is 12 to 15 per cent less when measured by labeled erythrocytes than when measured by a plasma tag (28) [Berson & Yalow (34); Brady *et al.* (35)]. Gregersen's summary of studies in splenectomized dogs by his group (36) and the discussion of Berson (1) give a clear exposition of the various aspects of this problem. The well known fact that the hematocrit of venous blood is too high because plasma is "trapped" among the erythrocytes has been investigated and summarized by Owen & Power (37). They and Chaplin & Mollison (38), Ebaugh, Levine & Emerson (39), and Hlad & Holmes (40) have elucidated the relationship of the trapped plasma to the centrifugal force and its duration. After correction for trapped plasma, the ratio of the body hematocrit to the venous hematocrit was approximately 0.89 in splenectomized dogs [Root *et al.* (41); Reeve *et al.* (42, 43)], and 0.88 and 0.95, respectively, in rats [Everett, Simmons & Lasher (44); Huang & Bondurant (45)]. In man the ratio was approximately 0.92 (28, 34, 35), constant over a wide hematocrit range, and 0.87 in premature infants [Schulman, Smith & Stern (46)]. A lower ratio has been found in certain states (see sections on pregnancy, shock, and cardiac failure). With splenomegaly the ratio may be higher than one (47, 48). The blood of large arteries and veins from various regions has the same content of cells [Hamilton & Horvath (49)]. Therefore, only the "small vessels," which occupy not more than 20 per cent of the total vascular space [Landis & Hortenstine (50)], remain as a location for the "extra plasma" found by the plasma tag methods. The distribution of labeled red cells and plasma in organs and tissues has been used to measure "the small vessel hematocrit" in dogs [Allen & Reeve (51); Gregersen, Cizek & Allen (52)], and in rats (44). A larger distribution space of the plasma tag compared to the red cell tag was found particularly in the kidneys (44, 51), but also in the bones, adrenals, and ovaries (44). The spleen (44, 51) and the thyroid gland (44) showed an excess of erythrocytes. The methods used would not unveil loss of

plasma tag in the early distribution phase. If the hypothesis of glomerular protein filtration is correct [Sellars *et al.* (53)], the "extra plasma" found in the kidney might be filtered albumin prior to reabsorption.

In any case, it is advisable to visualize the plasma space as less well defined than the red cell volume. In contrast to earlier reports, recent studies have showed good correspondence between results obtained with T-1824 and I^{131} labeled albumin [Schultz *et al.* (54); Freinkel *et al*, (55); Inkley *et al.* (56); Sear *et al.* (57)]. Technical improvements in the T-1824 and I^{131} methods have been offered by Allen *et al.* (58), Clausen & Lifson (59), Levey *et al.* (60), and Freinkel *et al.* (61). An interesting study by polarography [Markus & Baumberger (62)] may provide a new approach to the understanding of the T-1824-protein equilibrium. The introduction of Cr^{51} chloride for plasma labeling seems valuable [Frank & Gray (63)]. A promising report [Rodnan (64)] that plasma volume was 16.5 per cent smaller when measured with I^{131} labeled globulin than with T-1824 awaits confirmation.

Ten minutes appears to be minimum mixing time for reliable sampling (34). Continuous recording of radioactivity when blood was shunted from femoral artery to antecubital vein showed that mixing was completed in 4 to 15 min. (average 9) [Pritchard, Moir & MacIntyre (65)]. Mixing of carbon monoxide and T-1824 was complete within 15 min. during venous congestion of three extremities [Brown, *et al.* (66)]. In certain conditions, mixing may be delayed (see sections on temperature, cardiac insufficiency, and shock).

NORMAL VALUES, MAN AND ANIMALS

Average normal values of red cell volume (Fe^{55}, Fe^{59}, P^{32} and K^{42} methods) and of plasma volume (T-1824 and I^{131}) have been summarized by Berson (1). Gregersen & Nickerson (67) have surveyed measurements with T-1824 from 1915 to 1950.

Recent studies of normal values in women (P^{32} or Cr^{51}) show good correspondence of average volumes (ml. per kg. body weight) of red cells, 23.4 to 25.5, and of whole blood, 59 to 66.5 [(13, 15); Hedlund (68); Picón-Reátegui *et al.* (69); Wadsworth (70)]. Steinbeck (71) and Allen *et al.* (72) used T-1824. In men, average normal values (Cr^{51} or P^{32}) (ml. per kg.) for red cells are 27.8 to 30.9, and for total blood, 61.5 to 69.8 (2, 8, 9, 10, 13, 15, 16, 35, 68). Studies in premature infants (46) and in children of all ages have been published [CO method, Karlberg & Lind (73)].

Blood volume measurements are generally expressed in relation to body weight. Other referents such as height give approximately the same variability. Regression to weight and height combined reduces variability [Cr^{51}, Wennesland *et al.* (74)]. Relating blood volume in (Cr^{51} 32) normal subjects to weight, surface area or extracellular fluid volume (S^{35}) gave the same coefficient of variation for each referent (16). Regression to weight and the cube of height gave, for both sexes, the best predictability of volumes [T-1824, (72)]. Equations of multiple regressions for red cell volume to fat and to lean tissue reduced the variability very little; obesity tissue had about

two-thirds the blood content of lean tissue (15). Consideration of body types (after Sheldon) reduces only slightly the variability; age (19 to 52 years) has no apparent influence (74). Studies on growing animals and people are difficult to interpret because of changes in body composition. In animals compared to man the following species have large volumes per kg. body weight: dog (42) [Billings & Brown (75)]; horse, particularly the "hot blooded" race horses [Julian, *et al.* (76)]; and the White Pekin duck, a diving animal [Portman, McConnell & Rigdon (77)]. Low values have been found in the rat (44); [Loring (78)]; swine [Bush, and co-workers (79)]; and cow [Reynolds (80)]. However, if the weight of a cow is corrected for the 20 gallons its large stomach can contain, the average blood volume becomes about 75 ml. per kg. (80). The importance of age and growth is demonstrated in swine (79), where the smallest pigs (average 10 kg.) have values as high as that of the dog. In animal experiments the investigator may meet special difficulties, e.g., the spleen of the dog and other species can cause sudden changes in the distribution of the erythrocytes (36). The common methods have been thoroughly tested only in man and dog.

RESPONSE TO STRESS

Exercise and Physical Training

Radioisotope cell tags have not been used to measure volume changes directly during exercise, and technical difficulties make the use of dyes unsatisfactory for this purpose [Ebert & Stead (81)]. The hemocencentration seen during moderate exercise does not progress beyond 15 min. [Holmgren (82)].

Sjöstrand (4) found blood volume in relation to body weight 41 per cent above predicted normal in athletes trained for competition (CO method). Excellent correlation has been demonstrated between total hemoglobin and cardiac volume during rest, and the largest values for each were found in trained athletes of both sexes [Kjellberg, Rudhe & Sjöstrand (83)]. However, the carbon monoxide method used by these authors may not be well suited to study the effects of muscular development on the blood volume, because the gas combines with myoglobin, and the body's content of muscle pigments is increased by exercise and by hypoxia [Millikan (84); Vaughan & Pace (85)]. Analysis of our data shows that red cell volume in relation to height and weight (Cr^{51}) is only slightly larger in prison inmates accustomed to considerable physical activity than in those with sedentary habits (74).

Altitude and Hypoxia

This field has been reviewed by Stickney & Van Liere (86) and by Lawrence (87). In adaptation to high altitude, an increased rate of red cell formation is established without changes in the life span of the cells [see Lawrence (87) for references]. In Andean natives taken from 14,900 ft. to sea level, red cell production fell to 10 per cent of normal, a value similar

to that found in rats made plethoric by transfusion [Elmlinger, Huff & Oda (88)]. However, no significant change was observed in the red cell volume during the first 10 days [P^{32} (87)]. In rats exposed to simulated altitudes of 15,000 ft. for as long as 100 days [Fryers (89)], the rate of formation of new red cells (measured with Fe^{59}) increased 5.9 times immediately after exposure. This acceleration was not maintained. The ratio of blood volume to body weight became constant after 10 days at a value 20 per cent above normal. In rats acclimatized to 8,000, 15,000 and 20,000 ft., the red cell volumes were progressively higher. These increases were partially compensated for by reduction in plasma volume, but above 15,000 ft. no further reduction occurred (89).

In Peruvian natives acclimatized to sea level and 14,900 ft., respectively, volumes (ml. per kg., P^{32}) of red cells were 32.0 as contrasted with 47.5, and of whole blood 70.7 as contrasted with 83.5 (87). Earlier studies done with dye methods at 14,900 ft. have been confirmed [Monge *et al.* (90)].

An initial hemoconcentration occurs in persons transported rapidly from sea level to 14,900 ft. This is caused by loss of plasma rather than mobilization of cells (87). Lawrence (87) pointed to a possible analogy between this response and the clinical condition, "relative polycythemia," in which red cell volume is normal but plasma volume small. Acute hypoxia causes increased pressure in the small veins [Nahas, Josse & Muchow (91)]. This, by influencing capillary pressure, could cause movement of fluid from vascular to extravascular spaces, as observed by Arnould & Lamarche (92).

Environmental Temperature, Hypothermia and Hibernation

Effects of environmental temperature have been reviewed by Bass & Henschel (93). Seasonal changes of blood volume may be caused by changes of temperature or by other factors, such as the number of daylight hours, as suggested by Sjöstrand (4).

Effects of heat.—When subjects are kept hydrated and are active, a change from comfortable to hot and humid conditions leads to an increase in blood volume, which progresses to a maximum of 20 to 30 per cent in seven days (93). If exposure continues longer than seven days, blood volume returns to nearly normal [Bass *et al.* (94)]. Expansion of plasma volume appears responsible for changes observed during the first 14 days (93, 94); [Spealman, Newton & Post (95)]. Parallel changes occur in the extracellular fluid volume, but in the first days of heat exposure the intravascular compartment receives a relatively larger share of this increase than the interstitial space (94). The reported changes during the first hours after exposure to heat are slight, inconsistent, and possibly within the range of error of the dye-hematocrit method [Glickman *et al.* (96)]. None of the recent experiments in which environmental conditions were strictly controlled were continued long enough to determine the effects of prolonged heat exposure on erythropoiesis or red cell mass. In steelworkers subjected to furnace heat most of the day, no increase in the ratio of total hemoglobin to body weight

could be found [CO method, Lindholm (97)]. Participation of the venomotor system in the process of adaptation is suggested by results of plethysmographic studies [Whitney (98)]. The volume of the human forearm increased during early exposure to a hot and humid environment, but after repeated daily exposures forearm volumes decreased.

Effects of cold.—Decreased plasma volume causes slight hemoconcentration early during exposure to mild cold [Spealman *et al.* (95) Bass & Henschel (93)]. Conversely, most investigators have found normal plasma volumes in men fully acclimatized and working in the cold (93). Eskimos accustomed to outdoor life have higher than normal plasma and blood volumes [Brown *et al.* (99)]. Basal metabolic rate and resting blood flow in forearm and hand were also high in Eskimos compared to unacclimatized white subjects (99). Analogies were drawn between these findings and those occurring in hyperthyroidism, i.e., increases in resting oxygen consumption, blood volume, and peripheral blood flow (99).

Hypothermia.—Modest to large reductions of blood volume have been observed in dogs, chicks, and rabbits during hypothermia, but evidences of delayed or incomplete mixing of plasma and cell tags make the results doubtful (100, 101); [Rodbard *et al.* (102)]. Sircar (101) allowed 25 min. for mixing of T-1824 in dogs with rectal temperatures of 25 to 23 C. and found plasma and red cells both apparently reduced. D'Amato & Hegnauer (100) reported that mixing of T-1824 and P^{32} took 50 to 60 min. in dogs cooled by immersion to rectal temperatures of 22 to 20 C. Making allowance for this, they found plasma volume reduced by an average of 12 per cent, whereas red cell volumes and plasma protein concentrations were unchanged. They also observed a marked decrease in the ratio of body hematocrit to venous hematocrit (100).

Hibernation.—Svihla & Bowman (103) claimed that the blood volume falls from 59 ml. when awake to 25 ml. during dormancy in the ground squirrel. Spleen size may increase as much as 500 per cent in some species of bats during hibernation. Red cells and whole blood are rapidly returned to the circulation as the animals become active [Lidicker & Davis (104)].

Pregnancy

Burwell (105) has described the alterations in circulation and oxygen utilization which occur in pregnancy: the circulatory changes are analogous to those seen in cases of arteriovenous fistula. Increased cardiac output, blood volume, and peripheral blood flow provide for the nutritional requirements of the uterus and its contents and for heat loss. Recent studies with cell tags have confirmed, in general, that blood volume increases 20 to 30 per cent on the average during human pregnancy [P^{32}, Berlin, *et al.* (106)]; [CO method, Gemzell *et al.* (107)]. As had been noted before, considerable individual variation occurs (107). Berlin *et al.* (106), subjecting each of 181 women to a single determination at a different stage of pregnancy, con-

firmed the frequently reported observation that blood volume falls during the final weeks of pregnancy.

There is general agreement that the expansion of plasma volume is greater than that of cell volume (105, 106, 107). Anemias occurring during the latter half of pregnancy have sometimes been attributed to this hemodilution, but it has recently been shown that the hemoglobin concentration and red cell count remain within the limits of normal for nonpregnant women if adequate iron is supplied [Benstead & Theobald (108)]. Bantu women, who have a diet unusually high in iron, show no anemia during pregnancy [Gerritsen & Walker (109)].

Verel, Bury & Hope (110) using P^{32} and T-1824 simultaneously, found the ratio between body hematocrit and venous hematocrit much more variable than usual during the puerperium, and commented that findings may be misleading if based only on plasma volume or cell volume measurement and peripheral hematocrit.

Reynolds (111) used T-1824 to study 20 primiparous cows at various stages of pregnancy and during the first lactation. During gestation the cows showed increases in plasma and blood volumes, which were attributable in part to their maturing growth and in part to gestational processes. During lactation the increased volumes were maintained, so that blood volume, expressed in relation to body weight, was higher than during pregnancy. No anemia developed during pregnancy or lactation.

The blood content of the maternal and fetal portions of the placenta has been studied with P^{32} in guinea pigs [Fuchs (112)]. Maternal blood volume increased during pregnancy and fell toward term; the volume changes were more striking if expressed in terms of ml. per 100 gm. weight minus products of conception than in terms of total maternal weight. Mixing of tagged cells was complete at 5 min. in the maternal placenta, and there was no evidence of penetration of cells to the fetal side. The percentage of maternal red cell volume contained in the placenta rose to 10 per cent at the end of pregnancy. Injections of tagged cells into individual fetuses showed 11 to 18 per cent of fetal blood in the placenta.

DISEASE STATES

Arteriovenous Fistula

Frank *et al.* (113) measured separately the blood flow through an experimental arteriovenous shunt and through the remainder of the body. In fistulae accommodating flows greater than 27 per cent of control cardiac output, the output failed to increase by the full amount of fistula flow, and body flow decreased. Infusions of saline solution restored body flow to control levels. In dogs with chronic experimental fistulae, infusions of saline improved cardiac performance except in animals with very large shunts and failing hearts [Ferguson *et al.* (114)]. Epstein & Ferguson (115) found plasma

volume 20 per cent increased in dogs 14 to 42 days after opening arteriovenous communications (P^{32} and T-1824); red cell volume was not affected, and the ratio of body hematocrit to venous hematocrit was decreased. Hydremic plethora without increased cell volume was also observed in dogs studied at longer intervals after establishment of fistulae (3 to 40 weeks) [Lillehei, Bobb & Visscher (116)]; the average increase of plasma volume (37 per cent) accounted for about half the increase in observed thiocyanate space. In contrast, red cells and plasma contributed equally to the expansion of blood volume seen in patients before operative excision of large fistulae [Schreiner *et al.* (117); Warren, Elkin & Nickerson (118)]. It is not clear why simple plethora should occur in man and hydremic plethora in the dog. Holman's data (119) suggested increased red cell volumes in fistulous dogs. Circulating protein increases in proportion to plasma volume (116, 117, 118).

Cardiac Insufficiency

The relationship between disturbances of blood volume and the clinical syndrome of chronic congestive heart failure has been extensively investigated with radioactive cell tagging methods [Eisenberg (8); Reilly *et al.* (10); Gunton & Paul (13); Hedlund (68); Nylin & Hedlund (120); Prentice *et al.* (121); Ross *et al.* (122); Schreiber *et al.* (123); Povotskia & Tartakovskaia (124)] and CO methods (4, 125). Dogs with chronic failure due to lesions of pulmonic and tricuspid valves were studied (P^{32}) by Ross *et al.* (126). With two exceptions (122, 126), plasma and cell volumes appeared increased on the average in failure and tended to fall with clinical improvement. Although great variations exist, the average increase is about 20 per cent. The differences in reported values probably reflect differences in: (*a*) subjects (physical activity, nutritional status and medical management), (*b*) whether actual or edema-free weight is referred to, and (*c*) whether hematocrit values are corrected for trapping of plasma.

Simultaneous use of cell and plasma tags has shown that the ratio of body hematocrit to venous hematocrit may be lower than normal (122, 123). The marked discrepancies between cell tagging and plasma tagging methods have led to the claim that plasma tag methods may be unreliable in cardiac insufficiency (122). It is difficult to accept the alternate explanation that sufficient extra plasma may be contained in the small vessels of the viscera or elsewhere to account for a considerably lowered body hematocrit (123). Moir, Pritchard & Ford (127) looked for evidence of precocious loss of plasma tags in edematous patients. Although disappearance slopes for I^{131} were not abnormal, the possibility of exceptional losses during the early phases of mixing could not be excluded (127). Several reports have established that a longer than normal time is required for mixing of plasma tags (127) or labeled red cells (10, 120) in cardiac insufficiency, and failure to allow time for complete mixing may lead to erroneously low estimates of blood volume. The inability of Ross *et al.* (122, 126) to find increased volumes

cannot be accounted for in this way. In patients with cardiac insufficiency, blood volume correlates with cardiac volume (8, 68) [Nylin (128)], but not with venous pressure (68, 121) or severity of edema (8, 13, 121).

The relationship of the blood volume to the hemodynamic pattern of acute cardiac insufficiency has been studied in several animal preparations (129, 130, 131). The depressed cardiac output found in the shock-like state brought about in dogs by chemical injury to the myocardium was raised by infusions of dextran solution [Meyers, Schoolar & Overman (129)]. When a pump was substituted for the left ventricle of the dog, and right ventricular function was stopped, the system could not continue without the addition of blood to the circuit [Rose, Lazaro & Broida (130)]. Evidence of generalized vasoconstriction accompanied the 42 per cent fall in cardiac output that resulted from constriction of the pulmonary artery in dogs [Davis, Hyatt & Howell (131)]. Cardiac output improved concurrently with development of hydremic plethora in dogs surviving acute heart failure. Agress *et al.* (132) found blood volume (T-1824) 20 per cent below control values during protracted shock induced by embolization of the coronary arteries in dogs. These workers, however, like Meyers *et al.* (129), allowed such short intervals for mixing that they probably were measuring the "effective" rather than the entire blood volume. A number of investigators have noted normal plasma volumes during shock and acute heart failure following myocardial infarction [Freis *et al.* (133); Smith *et al.* (134); Gilbert *et al.* (135); Gammill *et al.* (136)].

Increased extracellular fluid resulting from renal conservation of sodium and water is a more constant feature of congestive heart failure than is increased plasma volume. Walser *et al.* (16) found the distribution of fluid between plasma and interstitial spaces shifted in favor of the latter. This can best be attributed to vasoconstriction. Rapidly accumulating evidence that venomotor tone is increased in heart failure has been summarized by Burch & Murtadha (137). Decreased vascular capacity would tend to keep venous pressure elevated and shrink plasma volume by promoting capillary filtration (50). No defect exists in the supply of albumin to the circulation [Bauman *et al.* (138)], so that loss of oncotic properties cannot account for the disproportionately small plasma volume. Signs of accelerated erythropoiesis found in many patients with heart failure have been attributed by Hedlund (68) to hypoxia.

Hepatic and Renal Diseases

An increase of plasma volume can be shown statistically in hepatic cirrhosis, although great variability is found between individuals. Results obtained with cell tags (139, 140) and with I^{131} (141, 142) or T-1824 (143) have not differed strikingly. According to Eisenberg (140) (Cr^{51}) and Cachera *et al.* (143) (T-1824), expansion of the plasma may be related to the presence of esophageal varices. Red cell volume was below normal in 20 of 28 cases studied by Hyde *et al.* (139) and in 17 of 42 studied by Cachera *et al.* (143).

Red cell volume was not significantly reduced in Eisenberg's 20 cases, but the inclusion of four patients with veno-arterial shunting and secondary polycythemia may have weighted the data.

The rates of disappearance of T-1824 and radio-iodinated albumin in liver disease are not greater than normal (143); [Tyor & Cayer (144)]. The amount of circulating albumin and its concentration are low (143); the size of the albumin pool and the rate of synthesis are reduced as measured with I^{131} [Oeff and Körtge (142); Eisenmenger (145)]. Increased concentration of gamma globulin can supply an oncotic effect sufficient to compensate for the low albumin concentration in cirrhosis (145).

Other circulatory needs, besides the large venous collateral system (140), demand increased blood volume. Abelmann *et al.* (146) have observed in some cirrhotics a hyperdynamic state similar to that seen in the presence of an arteriovenous fistula.

The increased plasma and blood volumes (T-1824) found in acute nephritis with edema [Cardozo (147)] may be caused by the heart failure common in such patients [Peters (148)]. We have not found plasma and blood volumes increased in acute nephritis without edema (125).

Steinbeck (149) has confirmed that the anemia of renal insufficiency reflects a reduction in red cell volume, which in turn is caused by diminished red cell production [Chaplin & Mollison (150)]. Red cell life span may be reduced in terminal nephritis (150) and compensatory plasmemia occurs (149).

Despite variable findings, some investigators believe that low blood volumes are most characteristic of the nephrotic state (149); [Squire (151)]. Using cell tags and T-1824, we found that the plasma and blood volumes of nephrotics were usually near normal, sometimes reduced and rarely increased; red cell volume was rarely decreased, except when renal failure was an added complication (125). In nephrosis, total circulating albumin and albumin pool are greatly reduced (145); [Blahd *et al.* (152); Gitlin *et al.* (153)]. The defect is caused by continued renal loss (145, 152, 153).

The variability of plasma volume in nephrosis and cirrhosis may be attributed to interaction of multiple factors compensating for the deficiency of circulating albumin, including increased extracellular fluid volume [Gilder *et al.* (141)], hyperglobulinemia in cirrhosis (143, 145), lipemia in nephrosis [Albrink *et al.* (154)], and possibly changes in the oncotic properties of serum proteins [Armstrong *et al.* (155)].

Vascular constriction is probably another compensatory factor, serving to maintain "effective" blood volume and blood pressure by reducing vascular capacity at times when plasma volume cannot be sustained because of protein deficit. The results of administering albumin intravenously to nephrotic patients illustrate this [Chinard *et al.* (156)].

Anemia and Polycythemia

A chronic reduction of the circulating red cell mass is usually compensated by an increase of plasma volume. The apparent accuracy of this

replacement depends on the methods of measurement and the standards used for predicting normal blood volume. Total blood volume was within the normal range when measured with P^{32} and dye in rabbits made anemic by molybdenum [Burke *et al.* (157)]. Blood volume was within two per cent of predicted in anemias of mixed etiology [Kleinsorg & Schaumann (158)] and slightly increased in anemias due to blood loss [Donner & Malý (159)]. Large individual variations may account for conflicting reports [Hallberg (160)]. Perhaps variations in venous tone may be accountable, since increased venomotor tone occurs in bled rabbits (161) and dogs [Alexander (162)]. During treatment of pernicious anemia, plasma volume falls as cell volume rises [CO method, (160)].

The plasmemia may be part of the circulatory adjustment to chronic anemia. Despite the over-all reduction of peripheral resistance, vasoconstriction occurs in the kidneys, with reduced renal blood flow [Whitaker (163)]. Rabbits made anemic by repeated hemorrhages showed no expansion of plasma volume unless the hemoglobin concentration was below 6 gm. per 100 mg. [Darian Smith & Simmonds (161)].

Lawrence's monograph (87) describes the results of extensive study of primary and secondary polycythemia by his group. Findings with regard to cell production and life span are the same as in the response to hypoxia. Red cell volume may be twice normal or higher [Wahlund (164); Abbatt *et al.* (165)]; Lawrence (87) shows some values approaching 100 ml. per kg. Plasma volume may decrease, but the whole blood volume is not as well controlled through this compensation as in anemia.

Shock, Hemorrhage, Syncope and Plasma Expanders

Shock has been the subject of two recent reviews [Frank (166); Millican & Rosenthal (167)] and several conference reports (168, 169). The fraction of the total blood volume contained in the splanchnic area in hemorrhagic shock may not be as great as previously supposed [Reynell *et al.* (170)]. The role of ferritin in perpetuating the shock syndrome has recently been questioned (166). Reeve (168) suggested that volumes smaller than predicted may be obtained with T-1824 in experimental shock. Mixing of cells tagged with P^{32} was not complete after two hours in dogs bled to shock levels [Delorme *et al.* (171)]. On the other hand, arteriovenous mixing times in the splanchnic circuit (I^{131}) were not prolonged in severely hypotensive dogs (170). Prentice and co-workers (172) found blood volume 15 per cent lower than predicted in battle casualties whose blood pressures had stabilized after transfusion (Cr^{51} and type "O" cells). The discrepancies between the large volumes transfused and the small volumes found could not be explained; mixing appeared to be complete, but the possibility existed that portions of the circulation were inaccessible to the tagged cells or dye (172). The ratio of body hematocrit to venous hematocrit (T-1824 and P^{32}) was normal in resuscitated battle casualties (172), but low in dogs with extensive burns [Salzberg *et al.* (173)]. T-1824 appears unreliable for use in burns because of protein leakage [Fogelman & Wilson (174)]. Radiotracer studies have shown that protein

accumulates in the damaged limbs of tourniquet-shocked mice, where it ceases to participate in protein exchange [Millican & Rosenthal (167); see also Fox *et al.* (175)].

The largest amounts of blood were required to resuscitate cases of extensive muscular injury of the extremities [Howard, *Third Macy Conference*, p. 9 (169)]. This is consistent with observations that about 60 per cent of the body's blood is in the muscles [Karpeles & Huff (176)]. The relationship between the muscular vasodilation during syncope in man and the shock syndrome is uncertain. Increased blood content of muscle has been found in dogs during hemorrhagic shock [Delorme (177)]. General anesthesia interferes with muscular vasodilation and with the marked reduction of renal blood flow that usually accompanies large venesections in man [de Wardener *et al.* (178)]. Alexander (162) demonstrated participation of the mesenteric veins in the constrictor response to hemorrhage, while Burch & Murtadha (137) noted a transient fall of forearm venomotor tone during psychically induced fainting.

Dextran infusions cause striking changes in the relative amounts of circulating albumin and globulin [Carbone *et al.* (179); Jaenike & Waterhouse (180)]. The immediate fall of plasma protein concentration following dextran infusion can be accounted for by the change in plasma volume [Greenman *et al.* (181)]. The great increases of plasma volume and circulating protein that occurred many days after large doses of dextran are not explained (180).

The diuresis that follows administration of dextran to normovolemic subjects is not accompanied by saluresis (180, 181). It is not due to the osmotic effect of dextran in the urine [Young (182)] and cannot be attributed to changes in renal circulatory dynamics (180, 182). Since diuresis does not regularly follow infusion of blood (182) or hyperoncotic albumin [Petersdorf & Welt (183)], the diuretic effect of dextran probably is not due to neurohumoral responses to expanding the blood volume. Errors may arise when volume measurements are attempted in the study of plasma expanders. Apparent changes in effective pore size of the capillaries and rapid recirculation of lymph have been described [Wasserman & Mayerson (184)]. Overexpansion of the circulation interferes with the use of plasma tags [Semple (185)]. The larger molecules of dextran produce adhesiveness of erythrocytes [Swank & Cullen (186)].

Miscellaneous Clinical Problems

Diseases characterized by weight change or deformity, such as rheumatoid arthritis, pose the problem of what reference standard to use in interpreting blood volume measurements. For this reason it is not clear whether the slight increase in plasma volume found by Jeffrey (187) and Dixon *et al.* (188) represents a true hydremic plethora. Red cell volume is frequently decreased in cancer [Cr^{51}, Reilly *et al.* (189); P^{32}, Berlin *et al.* (190)]. A number of anesthetic agents influence plasma volume only when venous or arterial pressures change materially [Price *et al.* (191)].

CONTROL MECHANISMS

The blood volume may be regarded from three points of view. The red cell mass is the means of transport for the respiratory gases. The plasma is part of the extracellular fluid. The total quantity of blood must accommodate to and be accommodated by the heart and vascular tree at all times. The vascular system responds to many forms of stress by rapid alteration in capacity, resulting in pressure changes. These, in turn, affect distribution of the blood, and adjust its volume by altering the balance of forces that influence fluid movement across the capillary walls so that the portion of extracellular fluid within the blood space is expanded or contracted (50). Receptors sensitive to changes in effective blood volume and taking part in the control of body fluids probably are located in or near the walls of the cardiovascular system [Gauer & Henry (6); Luetscher (192)]. The red cell volume responds chiefly to oxygen needs. When it deviates from normal, the circulatory system compensates by changing the volume of plasma. An example of reciprocal adjustment is found in animals with active spleens. The amount and speed of these changes determine the limits of compensation. In acute bleeding the most rapid movement of extracellular fluid into the blood stream may be insufficient. In extreme erythremia the reduction of plasma may reach a limit when increased intravascular viscosity seriously impairs peripheral blood flow [(89); Mendlowitz (193)].

Coleman *et al.* (194) have pointed out the importance of iron stores and iron supply in the regeneration of blood. Grant & Root (3) concluded that erythropoiesis could be stimulated experimentally only by anoxia or excessive cobalt and that the erythroid marrow does not respond directly to changes in oxygen tension.

No clear relationship has been demonstrated between the effect of cobalt and spontaneous regulation of erythropoiesis. Cobalt does not stimulate either oxygen consumption or heme synthesis in bone marrow *in vitro* [Laforet & Thomas (195)]. It may operate by interfering with enzymatic reduction systems, thus inducing a relative anoxia of tissues, including those controlling erythropoiesis [Shen & Ley (196)]. It does not influence the life span of the erythrocyte [Van Dyke *et al.* (197)].

The erythropoietic responses to hemorrhage and hypoxia are not influenced by extensive sympathectomy [Orahovats & Root (198); Grant & Root (199)]. The response to hypoxia was intensified by interrupting the buffer nerves from carotid and aortic areas of the dog (200), but had little or no effect on erythropoiesis without hypoxia [Terzioğlu *et al.* (200); Sisson *et al.* (201)].

Red cell volume is not well maintained in the absence of the anterior pituitary [Van Dyke *et al.* (202)] or adrenal cortex [Piliero & Pansky (203)]. The effects of hormones on blood volume are hard to determine because they also influence oxygen requirements and body size and composition [Gemzell & Sjöstrand (204, 205)].

In 1953 a pituitary factor capable of stimulating erythropoiesis was dis-

covered by Contopoulos, Van Dyke *et al.* (206, 207). Convincing demonstrations of the marrow stimulating effect of plasma from bled animals were reported at about the same time [see Erslev for summary (208)]. The plasma of bled animals must contain at least one active substance other than the pituitary factor, since the erythropoietic response is about the same in rats given plasma from hypophysectomized or nonhypophysectomized bled rats [Crafts & Meineke (209); Fried *et al.* (210)].

The source of the plasma factor is still unknown. Activity has been found in boiled filtrates of peripheral red cells and liver [Gordon, Piliero & Tannenbaum (211)]. The plasma of bled rabbits whose lymphatic and hematopoietic tissues had been damaged by nitrogen mustard was active [Erslev & Lavietes (212)]. Treatment with oxygen appears to reduce the effectiveness of otherwise active plasma and plasma extracts [Tohá *et al.* (213)]. Humoral substances capable of stimulating erythropoiesis have been detected not only in the blood of anemic animals of several species (208), but in the blood of rabbits subjected to hypoxia [Hirsjärvi (214)], of erythroblastotic infants [Seip (215)], of pregnant rats [Contopoulos *et al.*(216)], in cord blood of newborn infants (215); [Butzengeiger & Lange (217)], and in the milk of hypoxic rats and mice [Grant (218)].

Blood regeneration continues after hemorrhage, even though the cardiovascular response to anemia (high cardiac output and low over-all resistance) provides adequate oxygen to the tissues. Erslev (208) has proposed that some tissue not sharing in the increased blood flow may produce the plasma factor. The kidney might be such an organ. The means by which red cell volume becomes increased in conditions characterized by simple plethora, e.g., arteriovenous fistula, is not clear. No increase of plasma factor could be found in the blood of animals made hydremic by infusions of dextran [Erslev (219)].

Plasma volume may be altered by changes in one or more of the factors controlling fluid movement across the capillary bed, but equilibrium tends to be restored quickly. For example, fluid was filtered rapidly during the first part of a 30 min. period of general venous hypertension induced by Valsalva maneuvers, but during the next 20 min., filtration diminished or stopped while venous pressure was still elevated [Brown, *et al.* (220)]. The plasma volume does not accurately reflect changes in extracellular fluid volume [Levitt (221)]. The partition of extracellular fluid is altered in several pathologic states so as to maintain greater constancy of plasma than of interstitial fluid volume, e.g., in various forms of edema (221), [Aikawa (222)], in hypertension and in mild heart failure (16), [Teng *et al.* (223)], and following administration of ACTH and cortisone [Walser *et al.* (224)]. Only under extreme circumstances, such as extensive salt and water depletion, is the volume of the extracellular fluid insufficient to support the plasma volume (221), [Elkinton & Danowski (225)]. The total quantity of circulating protein, especially albumin, obviously is important in determining the amount of plasma, but little is known about how it is adjusted. The

anterior pituitary and the adrenal cortex have some influence on protein metabolism and distribution [White (226); Ulrich, Tarvrer & Li (227)]. Half to two thirds of the plasma protein traverses the thoracic duct daily [Forker *et al.* (228)]. Protein exchange is seriously disturbed in shock (167). In healthy adults, restoration of total circulating protein after loss of 1000 ml. of blood is usually accomplished in one week (194). The total body pool of protein is adequate for maintenance of plasma volume, except in starvation or disease, where synthesis is impaired or renal losses are extensive. About half the total albumin pool is intravascular, but disease may affect this distribution (138, 145, 152, 153). Although reduction of plasma albumin and of the store of labile protein can cause reduced plasma volume [Allison (229)], this is not found consistently, e.g., in starvation [Henschel *et al.* (230)]. (See section on hepatic and renal disease for discussion of the means by which plasma volume is sustained in spite of albumin depletion.) Caution must be used in interpreting measurements of plasma protein turnover and pool size, as emphasized by Luck (231), Volwiler *et al.* (232) and by Slater & Sass-Kortsak (233). Even the estimate of total circulating protein is no better than the measurement of plasma volume on which it is based. Lipides may displace as much as 20 per cent of the plasma water [Albrink (154)], but have little influence on osmotic pressure (154); [Popjak & McCarthy (234)].

The role of venomotor tone in adjusting the volume and distribution of the blood, and evidence that it is subject to variations, has been discussed earlier (137). Alexander (235) demonstrated reflexes causing increased capacity of the veins in response to increased load. Gauer, Henry & Sieker (236) found apparent constancy of venous tone over long periods. Central venous pressure changed proportionately with changes in blood volume induced by transfusing or bleeding about 10 per cent of blood volume in men(236). Pressure returned to resting levels only after blood volume was restored, and persistent pressure changes were thought capable of continuing to activate volume regulating mechanisms (6, 236).

The search for nervous receptors sensitive to changes in blood volume has been unproductive, except for the work of Paintal (237) and of Gauer, Henry and their associates (6, 236, 238, 239). An intracranial site for such receptors seems unlikely; Netravesish (240) noted no effect of neck compression on natriuresis or diuresis in sitting subjects. Sites in the head or the lower extremities appeared unlikely to Cathcart & Williams (241) because natriuresis and diuresis were not influenced by the head-down posture. However, changes of pressure in the limb veins can initiate local vaso-constrictive reflexes [Gaskell & Burton (242)]. The cat's vagus carries centripetal impulses influenced by changes of auricular distention rather than of pressure (237). Increased activity of similar vagal fibers in the dog was induced by maneuvers known to cause diuresis, such as inflation of a balloon in the left atrium, negative pressure breathing and expansion of the blood volume (239). Vagal cooling prevented the diuretic response (239).

Wherever the "volume receptors" may be, the kidney brings about the adjustment to changes in effective blood volume by changing the volume of extracellular fluid. Where blood volume is inadequate for the needs of the circulation (e.g., passive tilting, hemorrhage, heart failure, and acutely induced arteriovenous fistula), antidiuresis and sodium retention occur [Pearce & Newman (243); Epstein *et al.* (244); Hilton *et al.* (245)]. Hemodynamic and reflex effects are apparently less important than those due to changes in secretion of pituitary ADH and the corticosteroids, especially aldosterone [Goodyer & Jaeger (246); Judson *et al.* (247); Davis *et al.* (248)]. Overfilling of the thoracic vessels by negative pressure breathing influences only water excretion [(238); Surtshin *et al.* (249)], but it appears that aldosterone secretion is influenced by changes in blood volume (192) and by overhydration [Beck *et al.* (250)]. Phlebotomy of 8 ml. per kg. in man caused marked increases in the aldosterone-like activity of the urine and sodium retention, lasting one to two days [Fine, Meiselas & Auerbach (251)]. Increased secretion of an antidiuretic substance following venipuncture occurred only if subjects fainted, and was not related to the amount of blood withdrawn [Noble & Taylor (252)]. Thus, the role of the nervous system cannot be overlooked in studying this aspect of fluid control.

Among the most interesting developments during the past four years are: (*a*) the growing use of cell tags and simultaneous measurements of cell and plasma volumes; (*b*) demonstration of humoral factors influencing erythropoiesis; (*c*) illustration of the possible role of venomotor tone in influencing the volume and distribution of the blood; and (*d*) demonstration of intrathoracic receptors sensitive to volume change. Aldosterone probably will prove to play an important role in volume regulation. It is hoped that radioactive tagging methods and electrophoretic techniques will aid in solving the problem of how total circulating protein is controlled.

LITERATURE CITED

1. Berson, S. A., *Bull. N. Y. Acad. Med.*, **30,** 750 (1954)
2. Berlin, N. I., Hyde, G. M., Parsons, R. J., and Lawrence, J. H., *New Engl. J. Med.*, **247,** 675 (1952)
3. Grant, W. C., and Root, W. S., *Physiol. Revs.*, **32,** 449 (1952)
4. Sjöstrand, T., *Physiol. Revs.*, **33,** 202 (1953)
5. Sjöstrand, T., *Klin. Wochschr.*, **34,** 561 (1956)
6. Gauer, O. H., and Henry, J., *Klin. Wochschr.*, **34,** 356 (1956)
7. Sterling, K., and Gray, S. J., *J. Clin. Invest.*, **29,** 1604 (1950)
8. Eisenberg, S., *Circulation*, **10,** 902 (1954)
9. Nomof, N., Hopper, J., Jr., Brown, E., Scott, K., and Wennesland, R., *J. Clin. Invest.*, **33,** 1382 (1954)
10. Reilly, W. A., French, R. M., Lau, F. Y. K., Scott, K. G., and White, W. E., *Circulation*, **9,** 571 (1954)
11. Abajian, J., Jr., Brazell, E., Mills, E. L., and Peterson, O. S., Jr., *Anesthesiology*, **16,** 733 (1955)
12. Donohue, D. M., Motŭlsky, A. G., Giblett, E. R., Pirzio-Biroli, G., Viranuvatti, V., and Finch, C. A., *Brit. J. Haematol.*, **1,** 249 (1955)
13. Gunton, R. W., and Paul, W., *J. Clin. Invest.*, **34,** 879 (1955)
14. Mollison, P. L., and Veall, N., *Brit. J. Haematol.*, **1,** 62 (1955)
15. Huff, R. L., and Feller, D. D., *J. Clin. Invest.*, **35,** 1 (1956)
16. Walser, M., Duffy, B. J., Jr., and Griffith, H. W., *J. Am. Med. Assoc.*, **160,** 858 (1956)
17. Necheles, T. F., Weinstein, T. M., and LeRoy, G. V., *J. Lab. Clin. Med.*, **42,** 358 (1953)
18. Cooper, M., and Owen, C. A., Jr., *J. Lab. Clin. Med.*, **47,** 65 (1956)
19. Sutherland, D. A., and McCall, M. S., *Blood*, **10,** 646 (1955)
20. Hughes Jones, N. C., and Mollison, P. L., *Clin. Sci.*, **15,** 207 (1956)
21. Wennesland, R., Nomof, N., Hopper, J., Jr., and Brown, E., *Am. J. Med.*, **19,** 287 (1955)
22. Read, R. C., *New Engl. J. Med.*, **250,** 1021 (1954)
23. Reeve, E. B., *Brit. M. Bull.*, **8,** 181 (1952)
24. Hevesy, G., and Nylin, G., *Circulation Research*, **1,** 102 (1953)
25. Hevesy, G., and Nylin, G., *Acta Physiol. Scand.*, **24,** 285 (1952)
26. Yalow, R. S., and Berson, S. A., *Science*, **114,** 14 (1951)
27. Chaplin, H., Jr., *J. Physiol. (London)*, **123,** 22 (1954)
28. Chaplin, H., Jr., Mollison, P. L., and Vetter, H., *J. Clin. Invest.*, **32,** 1309 (1953)
29. Nickerson, J. L., Sear, H., and Reeve, E. B., *Am. J. Physiol.*, **175,** 230 (1953)
30. Cohen, J. A., and Warringa, M. G. P. J., *J. Clin. Invest.*, **33,** 459 (1954)
31. Sjöstrand, T., *Acta Physiol. Scand.*, **16,** 201 (1948)
32. Clark, J. T., Jr., *Am. J. Physiol.*, **162,** 560 (1950)
33. Sjöstrand, T., *Scand. J. Clin. Lab. Invest.*, **1,** 201 (1949)
34. Berson, S. A., and Yalow, R. S., *J. Clin. Invest.*, **31,** 572 (1952)
35. Brady, L. W., Cooper, D. Y., Colodzin, M., McClenathan, J. E., King, E. R., and Williams, R., *Surg. Gynecol. Obstet.*, **97,** 25 (1953)
36. Gregersen, M. I., *Am. J. Med.*, **15,** 785 (1953)
37. Owen, C. A., Jr., and Power, M. H., *J. Appl. Physiol.*, **5,** 323 (1953)

38. Chaplin, H., and Mollison, P. L., *Blood*, **7**, 1227 (1952)
39. Ebaugh, F. G., Levine, P., and Emerson, C. P., *J. Lab. Clin. Med.* **46**, 409 (1955)
40. Hlad, C. J., Jr., and Holmes, J. H., *J. Appl. Physiol.*, **5**, 457 (1953)
41. Root, W. S., Allen, T. H., and Gregersen, M. I., *Am. J. Physiol.*, **175**, 233 (1953)
42. Reeve, E. B., Gregersen, M. I., Allen, T. H., and Sear, H., *Am. J. Physiol.*, **175**, 195 (1953)
43. Reeve, E. B., Gregersen, M. I., Allen, T. H., Sear, H., and Walcott, W. W., *Am. J. Physiol.*, **175**, 204 (1953)
44. Everett, N. B., Simmons, B., and Lasher, E. P., *Circulation Research*, **4**, 419 (1956)
45. Huang, K. C., and Bondurant, J. H., *Am. J. Physiol.*, **185**, 441 (1956)
46. Schulman, J., Smith, C. H., and Stern, G., *Am. J. Diseases Children*, **88**, 567 (1954)
47. Verel, D., *Clin. Sci.*, **13**, 51 (1954)
48. Rothschild, M. A., Bauman, A., Yalow, R. S., and Berson, S. A., *J. Appl. Physiol.*, **6**, 701 (1954)
49. Hamilton, L. H., and Horvath, S. M., *Proc. Soc. Exptl. Biol. Med.*, **86**, 361 (1954)
50. Landis, E. M., and Hortenstine, J. C., *Physiol. Revs.*, **30**, 1 (1950)
51. Allen, T. H., and Reeve, E. B., *Am. J. Physiol.*, **175**, 218 (1953)
52. Gregersen, M. I., Cizek, L. J., and Allen, T. H., *Am. J. Physiol.*, **175**, 224 (1953)
53. Sellers, A. L., Griggs, N., Marmorston, J., and Goodman, H. C., *J. Exptl. Med.*, **100**, 1 (1954)
54. Schultz, A. L., Hammarsten, J. F., Heller, B. I., and Ebert, R. V., *J. Clin. Invest.*, **32**, 107 (1953)
55. Freinkel, N., Schreiner, G. E., and Athens, J. W., *J. Clin. Invest.*, **32**, 138 (1953)
56. Inkley, S. R., Brooks, L., and Krieger, H., *J. Lab. Clin. Med.*, **45**, 841 (1955)
57. Sear, H., Allen, T. H., and Gregersen, M. I., *Am. J. Physiol.*, **175**, 240 (1953)
58. Allen, T. H., Ochoa, M., Jr., Roth, R. F., and Gregersen, M. I., *Am. J. Physiol.*, **175**, 243 (1953)
59. Clausen, D. F., and Lifson, N., *Proc. Soc. Exptl. Biol. Med.*, **91**, 11 (1956)
60. Levey, S., Hower, J., and Loughridge, R. H., *J. Lab. Clin. Med.*, **41**, 316 (1953)
61. Freinkel, N., Schreiner, G. E., Athens, J. W., Hiatt, C. W., and Breese, S., *J. Lab. Clin. Med.*, **43**, 215 (1954)
62. Markus, G., and Baumberger, J. P., *J. Biol. Chem.*, **206**, 59 (1954)
63. Frank, H., and Gray, S. J., *J. Clin. Invest.*, **32**, 991 (1953)
64. Rodnan, G. P., *Clin. Research Proc.*, **4**, 90 (1956)
65. Pritchard, W. H., Moir, T. W., and MacIntyre, W. J., *Circulation Research*, **3**, 19 (1955)
66. Brown, E., Hopper, J., Jr., Sampson, J. J., and Mudrick, C., *J. Clin. Invest.*, **30**, 1441 (1951)
67. Gregersen, M. I., and Nickerson, J. L., *J. Appl. Physiol.*, **3**, 329 (1950)
68. Hedlund, S., *Acta Med. Scand.*, **146**, Suppl. 284, 1 (1953)
69. Picón-Reátegui, E., César Merino, M., Delgado Febres, E., and Hurtado, A., Acta Physiol. Latinoamer., **4**, 147 (1954)
70. Wadsworth, G. R., *Blood*, **9**, 1205 (1954)
71. Steinbeck, A. W., *Australian J. Exptl. Biol. Med. Sci.*, **32**, 95 (1954)
72. Allen, T. H., Peng, M. T., Chen, K. P., Huang, T. F., Chang, C., and Fang, H. S., *Metabolism*, **5**, 328 (1956)

73. Karlberg, P., and Lind, J., *Acta Paediat.*, **44,** 17 (1955)
74. Wennesland, R., Hodges, J. L., Jr., Hopper, J., Jr., Brown, E., Scott, K. G., Tucker, I. N., Guttentag, O., and Bradley, B. (In preparation)
75. Billings, H. H., and Brown, E. B., Jr., *Am. J. Physiol.*, **180,** 363 (1955)
76. Julian, L. M., Lawrence, J. H., Berlin, N. I., and Hyde, G. M., *J. Appl. Physiol.*, **8,** 651 (1956)
77. Portman, O. W., McConnell, K. P., and Rigdon, R. H., *Proc. Soc. Exptl. Biol. Med.*, **81,** 599 (1952)
78. Loring, W. E., *Proc. Soc. Exptl. Biol. Med.*, **85,** 350 (1954)
79. Bush, J. A., Jensen, W. N., Cartwright, G. E., and Wintrobe, M. M., *Am. J. Physiol.*, **181,** 9 (1955)
80. Reynolds, M., *Am. J. Physiol.*, **173,** 421 (1953)
81. Ebert, R. V., and Stead, E. A., Jr., *Proc. Soc. Exptl. Biol. Med.* **46,** 139 (1941)
82. Holmgren, A., *Scand. J. Lab. Clin. Invest.*, **8,** Suppl. 24, 1 (1956)
83. Kjellberg, S. V., Rudhe, U., and Sjöstrand, T., *Acta Physiol. Scand.*, **19,** 136 (1950)
84. Millikan, G. A., *Physiol. Revs.*, **19,** 503 (1939)
85. Vaughan, B. E., and Pace, N., *Am. J. Physiol.*, **185,** 549 (1956)
86. Stickney, J. C., and Van Liere, E. J., *Physiol. Revs.*, **33,** 13 (1953)
87. Lawrence, J. H., *Polycythemia* (Grune & Stratton, New York, N. Y., 136 pp., 1955)
88. Elmlinger, P. J., Huff, R. L., and Oda, J. M., *Proc. Soc. Exptl. Biol. Med.*, **79,** 16 (1952)
89. Fryers, G. R., *Am. J. Physiol.*, **171,** 459 (1952)
90. Monge, C., Cazorla, T. A., Whittembury, M. G., Sakata, B. Y., and Rizo-Patrón, C., *Acta Physiol. Latinoamer.*, **5,** 198 (1956)
91. Nahas, G. G., Josse, J. W., and Muchow, G. C., *Am. J. Physiol.*, **177,** 315 (1954)
92. Arnould, P., and Lamarche, M., *J. physiol.* (*Paris*) **46,** 809 (1954)
93. Bass, D. E., and Henschel, A., *Physiol. Revs.*, **36,** 128 (1956)
94. Bass, D. E., Kleeman, C. R., Quinn, M., Henschel, A., and Hegnauer, A. H., *Medicine*, **34,** 323 (1955)
95. Spealman, C. R., Newton, M., and Post, R. L., *Am. J. Physiol.*, **150,** 628 (1947)
96. Glickman, N., Fick, K. H., Keeton, R. W., and Montgomery, M. M., *Am. J. Physiol.*, **134,** 165 (1941)
97. Lindholm, A., *Arbeitsphysiol.*, **15,** 99 (1953)
98. Whitney, R. J., *J. Physiol.* (*London*), **125,** 1 (1954)
99. Brown, G. M., Bird, G. S., Boag, L. M., Delahaye, D. J., Green, J. E., Hatcher, J. D., and Page, J., *Metabolism*, **3,** 247 (1954)
100. D'Amato, H. E., and Hegnauer, A. H., *Am. J. Physiol.*, **173,** 100 (1953)
101. Sircar, P., *Proc. Soc. Exptl. Biol. Med.*, **87,** 194 (1954)
102. Rodbard, S., Saiki, H., Malin, A., and Young, C., *Am. J. Physiol.*, **167,** 485 (1951)
103. Svihla, A., and Bowman, H. C., *Am. J. Physiol.*, **171,** 479 (1952)
104. Lidicker, W. Z., and Davis, W. H., *Proc. Soc. Exptl. Biol. Med.*, **89,** 640 (1955)
105. Burwell, C. S., *Bull. Johns Hopkins Hosp.*, **95,** 115 (1954)
106. Berlin, N. I., Goetsch, C., Hyde, G. M., and Parsons, R. J., *Surg. Gynecol. Obstet.*, **97,** 173 (1953)
107. Gemzell, C. A., Robbe, H., and Sjöstrand, T., *Acta Obstet. et Gynecol. Scand.*, **33,** 289 (1954)

108. Benstead, N., and Theobald, G. W., *Brit. Med. J.*, **1,** 407 (1952)
109. Gerritsen, T., and Walker, A. R. P., *J. Clin. Invest.*, **33,** 23 (1954)
110. Verel, D., Bury, J. D., and Hope, A., *Clin. Sci.*, **15,** 1 (1956)
111. Reynolds, M., *Am. J. Physiol.*, **175,** 118 (1953)
112. Fuchs, F., *Acta Physiol. Scand.*, **28,** 162 (1953)
113. Frank, C. W., Wang, H., Lammerant, J., Miller, R., and Wégria, R., *J. Clin. Invest.*, **34,** 732 (1955)
114. Ferguson, T. B., Gregg, D. E., and Shadle, O. W., *Circulation Research*, **2,** 565 (1954)
115. Epstein, F. H., and Ferguson, T. B., *J. Clin. Invest.*, **34,** 434 (1955)
116. Lillehei, C. W., Bobb, J. R. R., and Visscher, M. B., *Surgical Forum, II*, 275 (1951)
117. Schreiner, G. E., Freinkel, N., Athens, J. W., and Stone, W., *Circulation Research*, **1,** 548 (1953)
118. Warren, J. V., Elkin, D. C., and Nickerson, J. L., *J. Clin. Invest.*, **30,** 220 (1951)
119. Holman, E., *Arteriovenous Aneurysm*, 14 (Macmillan Co., New York, N. Y., 244 pp., 1937)
120. Nylin, G., and Hedlund, S., *Am. Heart J.*, **33,** 770 (1947)
121. Prentice, T. C., Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S., *J. Clin. Invest.* **30,** 1471 (1951)
122. Ross, J. F., Chodos, R. B., Baker, W. H., and Freis, E. D., *Trans. A. Am. Physicians*, **65,** 75 (1952)
123. Schreiber, S. S., Bauman, A., Yalow, R. S., and Berson, S. A., *J. Clin. Invest.*, **33,** 578 (1954)
124. Povotskia, G. M., and Tartakovskaia, B. E., *Vestnik Rentgenol. i Radiol.*, No. 5, 29, Sept.–Oct. (1955)
125. Brown, E., Hopper, J., Jr., and Wennesland, R. (Unpublished data)
126. Ross, J. F., Barger, A. C., Finch, S. C., Ross, R. S., Price, H. L., and Freireich, E. J., *Trans. Assoc. Am. Physicians*, **66,** 289 (1953)
127. Moir, T. W., Pritchard, W. H., and Ford, A. B., *J. Lab. Clin. Med.*, **47,** 503 (1956)
128. Nylin, G., *Am. Heart J.*, **49,** 803 (1955)
129. Meyers, F. H., Schoolar, J. C., and Overman, R. R., *Circulation Research*, **2,** 304 (1954)
130. Rose, J. C., Lazaro, E. J., and Broida, H. P., *Circulation Research*, **4,** 173 (1956)
131. Davis, J. O., Hyatt, R. E., and Howell, D. S., *Circulation Research*, **3,** 252 (1955)
132. Agress, C. M., Rosenburg, M. J., Binder, M. J., Schniederman, A., and Clark, W. G., *Am. J. Physiol.*, **166,** 603 (1951)
133. Freis, E. D., Schnaper, H. W., Johnson, R. T., and Schreiner, G. E., *J. Clin. Invest.*, **31,** 131 (1952)
134. Smith, W. W., Wikler, N. S., and Fox, A. C., *Circulation*, **9,** 352 (1954)
135. Gilbert, R. P., Goldberg, M., and Griffin, J., *Circulation*, **9,** 847 (1954)
136. Gammill, J. F., Applegarth, J. J., Reed, C. E., Fernald, J. D., and Antenucci, A. J., *Ann. Internal Med.*, **43,** 100 (1955)
137. Burch, G. E., and Murtadha, M., *Am. Heart J.*, **51,** 807 (1956)
138. Bauman, A., Rothschild, M. A., Yalow, R. S., and Berson, S. A., *J. Clin. Invest.*, **34,** 1359 (1955)

139. Hyde, G. M., Berlin, N. I., Parsons, R. J., Lawrence, J. H., and Port, S., *J. Lab. Clin. Med.*, **39,** 347 (1952)
140. Eisenberg, S., *Am. J. Med.*, **20,** 189 (1956)
141. Gilder, H., Redo, S. F., Barr, D., and Child, G. C., III., *J. Clin. Invest.*, **33,** 555 (1954)
142. Oeff, K., and Körtge, P., *Klin. Wochschr.*, **34,** 75 (1956)
143. Cachera, R., Darnis, F., and Lepercq, G., *Presse méd.*, **59,** 1660 (1951)
144. Tyor, M. P., and Cayer, D., *J. Lab. Clin. Med.*, **39,** 874 (1952)
145. Eisenmenger, W. J., *Med. Clin. N. Amer.*, **39,** 719 (1955)
146. Abelmann, W. H., Kowalski, H. J., and McNeely, W. F., *J. Clin. Invest.*, **34,** 690 (1955)
147. Cardozo, E. L., *Acta Med. Scand.*, **125,** 333 (1946)
148. Peters, J. P., *Am. J. Med.*, **14,** 448 (1953)
149. Steinbeck, A. W., *Clin. Sci.* **12,** 327 (1953)
150. Chaplin, H., Jr., and Mollison, P. L., *Clin. Sci.*, **12,** 351 (1953)
151. Squire, J. R., *Advances in Internal Med.*, **7,** 201 (1955)
152. Blahd, W. H., Fields, M., Goldman, R., *J. Lab. Clin. Med.*, **46,** 747 (1955)
153. Gitlin, D., Janeway, C. A., and Farr, L. E., *J. Clin. Invest.*, **35,** 44 (1956)
154. Albrink, M. J., Hald, P. M., Man, E. B., and Peters, J. P., *J. Clin. Invest.*, **34,** 1483 (1955)
155. Armstrong, S. H., Jr., Kark, R. M., Schoenberger, J. G., Shatkin, J., and Sights, R., *J. Clin. Invest.*, **33,** 297 (1954)
156. Chinard, F. P., Lauson, H. D., Eder, H. A., and Greif, R. L., *J. Clin. Invest.*, **33,** 629 (1954)
157. Burke, J. D., Arrington, T. R., and Davis, G. K., *Blood*, **8,** 1105 (1953)
158. Kleinsorg, H., and Schaumann, W., *Deut. Arch. klin. Med.*, **201,** 266 (1954)
159. Donner, L., and Malý, V., *Sbornik Lékařský*, **57,** 125 (1955)
160. Hallberg, L., *Scand. J. Clin. Lab. Invest.*, **7,** Suppl. 16, 1 (1955)
161. Darian Smith, I., and Simonds, W. J., *Australian J. Exptl. Biol. Med. Sci.*, **32,** 241 (1954)
162. Alexander, R. S., *Circulation Research*, **3,** 181 (1955)
163. Whitaker, W., *Quart. J. Med.*, **25,** 175 (1956)
164. Wahlund, H., *Acta Med. Scand.*, **150,** 199 (1954)
165. Abbatt, J. D., Chaplin, H., Darte, J. M. M., and Pitney, W. R., *Quart. J. Med.*, **23,** 91 (1954)
166. Frank, H. A., *New Engl. J. Med.*, **249,** 445, 486 (1953)
167. Millican, R. C., and Rosenthal, S. M., *Ann. Rev. Med.*, **5,** 285 (1954)
168(a) Shock Syndrome, *Ann. N. Y. Acad. Sci.*, **55,** 347–542 (1952); (b) (Reeve, E. B., p. 351)
169. Shock & Circulatory Homeostasis, Trans. 1st, 2nd, 3rd & 4th Conf. (Green, H. D., Ed., Josiah Macy, Jr. Foundation, New York, N. Y., 1952–1955)
170. Reynell, P. C., Marks, P. A., Chidsey, C., and Bradley, S. A., *Clin. Sci.*, **14,** 407 (1955)
171. Delorme, E. J., Mukherjee, S. R., and Rowlands, S., *Quart. J. Exptl. Physiol.*, **37,** 107 (1952)
172. Prentice, T. C., Olney, J. M., Jr., Artz, C. P., and Howard, J. M., *Surg. Gynecol. Obstet.*, **99,** 542 (1954)

173. Salzberg, A. M., and Evans, E. I., *Ann. Surg.*, **132,** 746 (1950)
174. Fogelman, M. J., and Wilson, B. J., *Surg. Forum*, **5,** 762 (1954)
175. Fox, C. L., Lasker, S. E., Winfield, J. M., and Mersheimer, W. L., *Ann. Surg.*, **140,** 524 (1954)
176. Karpeles, L. M., and Huff, R. L., *Circulation Research*, **3,** 483 (1955)
177. Delorme, E. J., *Quart. J. Exptl. Physiol.*, **38,** 47 (1953)
178. de Wardener, H. E., Miles, B. E., Lee, G. de J., Churchill-Davidson, H., Wylie, D., and Sharpey-Schafer, E. P., *Clin. Sci.*, **12,** 175 (1953)
179. Carbone, J. V., Uzman, L. L., and Plough, I. C., *Proc. Soc. Exptl. Biol. Med.*, **90,** 68 (1955)
180. Jaenike, J. R., and Waterhouse, C., *Circulation*, **11,** 1 (1955)
181. Greenman, L., Fergus, E. B., Mateer, F. M., Weigand, F. A., and Danowski, T. S., *J. Appl. Physiol.*, **6,** 79 (1953)
182. Young, I. E., *Canad. J. Biochem. Physiol.*, **33,** 800 (1955)
183. Petersdorf, R. G., and Welt, L. G., *J. Clin. Invest.*, **32,** 283 (1953)
184. Wasserman, K., and Mayerson, H. S., *Circulation Research*, **3,** 594 (1955)
185. Semple, R. E., *Am. J. Physiol.*, **176,** 113 (1954)
186. Swank, R. L., and Cullen, C. F., *Proc. Soc. Exptl. Biol. Med.*, **82,** 381 (1953)
187. Jeffrey, M. R., *Blood*, **8,** 502 (1953)
188. Dixon, A. S., Ramcharan, S., and Ropes, M. W., *Ann. Rheumatic Diseases (London)*, **14,** 51 (1955)
189. Reilly, W. A., Helwig, H. L., and Scott, K. G., *Cancer*, **9,** 273 (1956)
190. Berlin, N. I., Hyde, G. M., Parsons, R. J., and Lawrence, J. H., *Cancer*, **8,** 796 (1955)
191. Price, H. L., Helrich, M., and Conner, E. H., *J. Clin. Invest.*, **35,** 125 (1956)
192. Luetscher, J. A., Jr., *Advances in Internal Med.*, **8,** 155 (1955)
193. Mendlowitz, M., *The Digital Circulation*, 142 (Grune & Stratton, New York, N. Y., 182 pp., 1954)
194. Coleman, D. H., Stevens, A. R., Jr., Dodge, H. T., and Finch, C. A., *Arch. Internal Med.*, **92,** 341 (1953)
195. Laforet, M. T., and Thomas, E. D., *J. Biol. Chem.*, **218,** 595 (1956)
196. Shen, S. C., and Ley, A. B., *J. Clin. Invest.*, **33,** 1560 (1954)
197. Van Dyke, D. C., Asling, C. W., Berlin, N. I., and Harrison, R. G., *Proc. Soc. Exptl. Biol. Med.*, **88,** 488 (1955)
198. Orahovats, P. D., and Root, W. S., *Am. J. Physiol.*, **173,** 324 (1953)
199. Grant, W. C., and Root, W. S., *Am. J. Physiol.*, **173,** 321 (1953)
200. Terzioğlu, M., Göral, C., and Bardavit, J., *Am. J. Physiol.*, **182,** 100 (1955)
201. Sisson, G., Cain, A., and Root, W. S., *Am. J. Physiol.*, **180,** 485 (1955)
202. Van Dyke, D. C., Garcia, J. F., Simpson, M. E., Huff, R. L., Contopoulos, A. N., and Evans, H. M., *Blood*, **7,** 1017 (1952)
203. Piliero, S. J., and Pansky, B., *Acta Haematol.*, **14,** 240 (1955)
204. Gemzell, C. A., and Sjöstrand, T., *Acta Endocrinol.*, **16,** 6 (1954)
205. Gemzell, C. A., and Sjöstrand, T., *Acta Endocrinool.*, **21,** 86 (1956)
206. Contopoulos, A. N., Van Dyke, D. C., Simpson, M. E., Garcia, J. F., Huff, R. L., Williams, B. S., and Evans, H. M., *Blood*, **8,** 131 (1953)
207. Van Dyke, D. C., Contopoulos, A. N., Williams, B. S., Simpson, M. E., Lawrence, J. H., and Evans, H. M., *Acta Haematol.*, **21,** 203 (1954)

208. Erslev, A. J., *Blood*, **10**, 954 (1955)
209. Crafts, R. C., and Meineke, H. A., *Proc. Soc. Exptl. Biol. Med.*, **92**, 223 (1956)
210. Fried, W., Plzak, L., Jacobson, L. O., and Goldwasser, E., *Proc. Soc. Exptl. Biol. Med.*, **92**, 203 (1956)
211. Gordon, A. S., Piliero, S. J., and Tannenbaum, M., *Am. J. Physiol.*, **181**, 585 (1955)
212. Erslev, A. J., and Lavietes, P. H., *Blood*, **9**, 1055 (1954)
213. Tohá, J., Eskuche, I., Abarca, F., Salvatore, F., and Hodgson, G., *Nature*, **175**, 167 (1955)
214. Hirsjärvi, E., *Acta Physiol. Scand.*, **34**, 338 (1955)
215. Seip, M., *Acta Paediat.*, **44**, 507 (1955)
216. Contopoulos, A. N., Van Dyke, D. C., and Simpson, M. E., *J. Clin. Endocrinol.*, **15**, 841 (1955)
217. Butzengeiger, K. H., and Lange, J., *Klin. Wochschr.*, **30**, 647 (1952)
218. Grant, W. C., *Blood*, **10**, 334 (1955)
219. Erslev, A. J., *Blood*, **10**, 616 (1955)
220. Brown, E., Hopper, J., Jr., Mudrick, C., and Sampson, J. J., *Am. J. Med.*, **5**, 618 (1948)
221. Levitt, M. F., *J. Mt. Sinai Hosp.*, **19**, 571 (1952–53)
222. Aikawa, J. K., *Am. J. Med. Sci.*, **224**, 632 (1952)
223. Teng, H. C., Shapiro, A. P., and Grollman, A., *Metabolism*, **3**, 405 (1954)
224. Walser, M., Seldin, D. W., and Burnett, C. H., *Am. J. Med.*, **18**, 454 (1955)
225. Elkinton, J. R., and Danowski, T. S., *The Body Fluids*, 157 (Williams & Wilkins, Baltimore, 626 pp., 1955)
226. White, A., "Effects of Hormones on Protein Metabolism," in *Hormones and the Aging Process*, 127 (E. T. Engle and G. Pincus, Eds., Academic Publishers, Inc., New York, N. Y., 323 pp., 1956)
227. Ulrich, F., Tarver, H., and Li, C. H., *J. Biol. Chem.*, **209**, 117 (1954)
228. Forker, L., Chaikoff, I. L., and Reinhardt, W. O., *J. Biol. Chem.*, **197**, 625 (1952)
229. Allison, J., *Physiol. Revs.*, **35**, 664 (1955)
230. Henschel, A., Mickelsen, O., Taylor, H. L., and Keys, A., *Am. J. Physiol.*, **150**, 170 (1947)
231. Luck, J. M., *Am. J. Med.*, **20**, 317 (1956)
232. Volwiler, W., Goldsworthy, P. D., MacMartin, M. P., Wood, P. A., Mackay, I. R., and Fremont-Smith, K., *J. Clin. Invest.*, **34**, 1126 (1955)
233. Slater, R. J., and Sass-Kortsak, A., *Am. J. Med. Sci.*, **231**, 669 (1956)
234. Popjak, G., and McCarthy, E. F., *Biochem. J.*, **40**, 789 (1946)
235. Alexander, R. S., *Circulation Research*, **4**, 49 (1956)
236. Gauer, O. H., Henry, J. P., and Sieker, H. O., *Circulation Research*, **4**, 79 (1956)
237. Paintal, A. S., *J. Physiol.* (*London*), **120**, 596 (1953)
238. Sieker, H. O., Gauer, O. H., and Henry, J. P., *J. Clin. Invest.*, **33**, 572 (1954)
239. Henry, J. P., and Pearce, J. W., *J. Physiol.* (*London*), **131**, 572 (1956)
240. Netravesish, V., *J. Appl. Physiol.*, **5**, 544 (1953)
241. Cathcart, E. S., and Williams, I. T. D., *Clin. Sci.*, **14**, 121 (1955)
242. Gaskell, P., and Burton, A. C., *Circulation Research*, **1**, 27 (1953)
243. Pearce, M. L., and Newman, E. V., *J. Clin. Invest.*, **33**, 1089 (1954)
244. Epstein, F. H., Post, R. S., and McDowell, M., *J. Clin. Invest.*, **32**, 233 (1953)

245. Hilton, J. G., Kanter, D. M., Hays, D. R., Bowen, E. H., Golub, J. R., Keating, J. H., and Wégria, R., *J. Clin. Invest.*, **34,** 732 (1955)
246. Goodyer, A. V. N., and Jaeger, C. A., *Am. J. Physiol.*, **180,** 69 (1955)
247. Judson, W. E., Hollander, W., Hatcher, J. D., and Halperin, M. H., *J. Clin. Invest.*, **34,** 1546 (1955)
248. Davis, J. O., Howell, D. S., and Hyatt, R. E., *Am. J. Physiol.*, **183,** 263 (1955)
249. Surtshin, A., Hoeltzenbein, J., and White, H. L., *Am. J. Physiol.*, **180,** 612 (1955)
250. Beck, J. C., Dyrenfurth, I., Giroud, C., P., Venning, E. H., and Browne, J. S. L., *Trans. Assoc. Am. Physicians*, **68,** 205 (1955)
251. Fine, D., Meiselas, L. E., and Auerbach, T., *Clin. Research Proc.*, **4,** 126 (1956)
252. Noble, R. L., and Taylor, N. B. G., *J. Physiol.* (*London*), **122,** 220 (1953)

PERIPHERAL CIRCULATION[1,2]

By Lysle H. Peterson[3]

Department of Physiology, School of Medicine, University of Pennsylvania
Philadelphia, Pennsylvania

Introduction

It is a truism that the "laws" governing the behavior of any physical system containing n variables can only be expressed and solved if it is possible to formulate n simultaneous, independent equations between the n variables. It is implicit that the variables are known.

Annually there appear, in the literature, data and concepts which are termed "controversial" and thereby achieve a certain negative status. Progressive research inevitably exposes new variables and the limitations of accepted physiological laws. It is probable, moreover, that often the controversial nature of new evidence reflects the tendency of physiologists to propose laws and principles prematurely.

The Extremities

The limbs have been the subject of many investigations and considerations during the past year. The limbs have special functions: temperature regulation, locomotion, and possibly regulation of posture-gravity effects. The "organs" of the limbs, skin and muscle, appear to have separate and characteristic functional properties which, whether properly or not, are often generalized as characterizations of all such tissue in the body. The literature with respect to the limbs also exemplifies another variable: methodology. Indirect methods for measuring blood flow depend upon the function of the organ while, at the same time, they may alter the organ's function. During a discussion primarily devoted to the limbs, Barcroft wisely asked " . . . why is it that different methods give different results . . . ?" (1).

In the limbs the responses associated with infusions of epinephrine and norepinephrine, as measured by VO Pleth., are generally agreed upon by most workers (1 to 4). On the basis of these observations it seems generally

[1] This survey includes the literature available to the author to the end of June, 1956.

[2] Abbreviations used throughout this chapter are: VO Pleth. (venous occlusion plethysmography); I^{131} HSA (human serum albumin iodinated with I^{131}); AVA (arteriovenous anastomosis); PAH (para-aminohippuric acid); ADP (adenosinediphosphate); ATP (adenosinetriphosphate); VDM (vasodepressor material); EEG (electroencephalogram); ACTH (adrenocorticotropic hormone); CBF (cerebral blood flow); Sp. BV (splanchnic blood volume); Sp. BF (splanchnic blood flow); BSP (bromosulphaphthalein); PBF (portal venous blood flow); PBP (portal venous blood pressure); Pu AP (pulmonary artery pressure); LAP (left atrial pressure).

[3] The author wishes to thank Miss E. Carolyn Taylor for her generous assistance in editing this review and Miss D. Deemer for her secretarial help.

concluded that the direct action of epinephrine on skin vessels is constrictor, and it has been suggested that there may be an indirect effect producing dilation due to inhibition of the vasomotor center by epinephrine (1). It seems agreed, too, that the direct action of epinephrine on muscle vessels is dilator in small doses but constrictor in large doses, although in the higher doses the effect may not be direct. It has also been suggested that the dilation of muscle vessels associated with epinephrine may be indirectly caused by lactic acid. More recently it was reported that the primary rise in muscle blood flow (VO Pleth.) associated with epinephrine given by artery or vein is not accompanied by an increase in muscle venous lactic acid, whereas there is an increase during the secondary rise in blood flow associated with intravenous epinephrine infusions (2, 3). It may be that the primary response is a direct action of epinephrine on the vessels, whereas the secondary response is associated with an epinephrine-induced reflex stimulation of skeletal muscle (1). It has also been reported that the increase in forearm flow (VO Pleth.), calculated to be due to vessel dilation,[4] during intravenous infusions of vasopressin (beta hypophamine, Pitressin) was not accompanied by an increase in the muscle venous lactic acid content (5). Norepinephrine appears to be a constrictor to both skin and muscle.

Cutaneous block[5] of the forearm, under certain conditions, does not alter the total apparent blood flow therein. Brachial, radial, and ulnar block approximately doubles flow, and, interestingly, brachial plexus block quadruples flow (VO Pleth.). Although the involved pathways have not been elucidated, it is possible that nerves, arising from the brachial plexus, may accompany the vessels themselves (6). The fact that cutaneous block does not produce a significant change in forearm flow has been assumed to be an indication that changes occurring in flow are mainly in the muscle vessels; however, it has been reported that heating the feet and legs caused an increase in forearm flow that was said to be in the skin (7).

Experimental evidence concerning the existence of vasodilator fibers to skin vessels continues to be controversial following application of VO Pleth. to the problem. Blood flow in the forearm was found not to increase during indirect body heating if cutaneous nerves were blocked[5] (8). In another study, indirect heating during anesthesia of mixed nerves (9), or intra-arterial injection of atropine (10) was not associated with an increased hand blood flow. It has also been reported that combined direct and indirect heating caused a greater increase in hand blood flow than did each independently (11). No quantitative relationships could be found between radiant heat exchange from the body and variations in blood flow (12).

[4] In this review vasopressin (Pitressin) is referred to both as a dilator and constrictor of muscle vessels and as having complex action on receptors and in the central nervous system. In this study the dose was only 170 milliunits per min., whereas in other studies the doses were considerably larger.

[5] Intra- and subcutaneous injections of anesthetic agents about limb circumference. The effectiveness of nerves blocked is difficult to assess.

Since many studies involve sympathectomized limbs, the question of vascular postsympathectomy hypersensitivity to epinephrine and norepinephrine continues to arise. Previous evidence (obtained by VO Pleth.) suggests that sensitivity is increased only in about 60 per cent of subjects (1). More recent evidence suggests an even smaller ratio (6: 13), and does not substantiate Cannon's "law" (13). It was concluded that substantial evidence is lacking for the theory that the opposing effects of acetylcholine, normally secreted into vessel walls, are removed by sympathectomy (14). Even more recently, however, additional evidence gives credence to this theory (15, 16). We are reminded that sympathetic synapses may be found in the ventral roots that remain after extirpation of the sympathetic chain (14).

Reactive hyperemia is another variable in methodology as well as an interesting physiological event. Results of attempts to standardize its production have indicated that the cause is "some" dilator substance whose effect is a function of transcapillary diffusion (17). Forearm hyperemia resulting from 3 min. of circulatory arrest could not be blocked by various antihistaminics, whereas that following longer arrest periods could be attenuated by such agents (18). Perfusion of histamine into isolated rabbit hind limbs produced both "constriction" and edema; but antihistaminics inhibited only the constriction (19). An additional factor in the production of reactive hyperemia may be a myogenic (or local reflex) response to reduced transmural pressure. Results obtained by increasing the latter during circulatory arrest support this suggestion; however, the mechanism is not as yet known (20).

The effects of variations of transmural pressure on intravascular pressure and flow have been the subject of many experiments, the rallying point of which is Bayliss' hypothesis that, when transmural pressure changes, some vascular response is involved which tends to maintain a constant blood flow. Therefore, studies of the limbs in the gravity field have been popular. Recent VO Pleth. studies have confirmed similar previous work, indicating that is the dependent position blood flow tends to decrease (21). If the limb vessels are considered analogous to a distensible U-tube and hydrostatic conditions are assumed, such results suggest myogenic reactivity or local reflexes, since this increase in calculated "resistance" has also been found to occur in sympathectomized limbs. Some uncertainties accompanying the use of the VO Pleth. under these conditions have been re-emphasized (22). In defense of the method it is reported that intravenous iodopyracet (Diodrast) does not leak under the collecting cuff; varying cuff pressure from 75 to 110 mm. Hg does not change estimated flow; and the plethysmograph volume change, with respect to time, is linear (21). The logic of such an argument escapes this author. The simplest concept of the method implies that the blood flows into the limb segment through arteries, then "resistance" vessels and hence into the veins, and does not escape. In such a system if volume changes at a constant rate, and if "resistance" is fixed, then the pressure everywhere must rise simultaneously and directly with time and flow rate. If flow and arterial

pressure remain constant, then, since venous pressure must rise, resistance must fall. It is also important to recall that it has been shown indirectly that increases in venous pressure were 5 to 10 times more effective in raising capillary pressure than equal increases in arterial pressure (23) which implies that the flow resistance is higher on one side of the "U-tube." Thus, in such a system it may not be correct to apply hydrostatic concepts. It seems very difficult to predict just what changes in flow would be expected in the dependent limb even if there were no reactive phenomena. Another important variable is the pressure-volume relationships of the distensible parts of the limb. An attempt has been made to obtain estimates of this by measuring the difference in volume of the forearm subjected to an external pressure varying between +200 and −100 mm. Hg for one minute. The relationships were nonlinear and the "capacity" did not change with variations of estimated blood flow rates. It was concluded that vascular contractility in the highest resistance vessels does not affect capacity (24). It is also possible that tissues other than blood vessels determine the capacity of the limb; therefore skeletal muscle contraction may alter capacity. It has been reported that, using a plethysmographic method, the veins of the forearm constrict in response to venous distention in the leg (25). Experiments have strongly supported the view that the VO Pleth. "after-drop" is not due to vessel contraction but rather is an "artifact" associated with cuff size, position, and pressure and with venous pressure (26, 27). It has been implied that problems remain in applying and interpreting digital "rheoplethysmography" (28).

It has been shown that heat elimination from the fingers is not essentially different in the dependent and horizontal position of the arm (29). Recently this method of estimating blood flow has been combined with the technique of varying transmural pressure by applying external positive and negative pressures to the limb for 10 min. In the dependent hand, heat elimination did not change until −60 to −100 mm. Hg was applied, whereupon it became reduced; at −200, however, heat elimination increased (22). In the toes, even −200 mm. Hg did not result in a significant change in heat elimination (30). When vascular distention was produced by an inflated wrist cuff, heat elimination from the fingers was reduced in proportion to the increase in venous pressure (31). It would appear from this series of studies that vascular resistance does not change significantly within normal ranges of transmural pressure change. In the calf, blood flow (VO Pleth.) was decreased following exposures to all pressures from −50 to −200 mm. Hg (32). The relationships between internal temperature and heat transfer have been found to be approximately linear in the thumb pad (33). The relationship between skin temperature and blood flow has been described as a family of nonlinear curves each with a scatter of points and each dependent upon the environmental temperature (34). Characteristics of heat passage from various flowing liquids to tube walls have been investigated (35).

It was suggested that arteriovenous oxygen difference of muscle blood may not be a reliable index of flow, since experimental results implied either

that muscle oxygen uptake is not constant or that variations in admixture with skin blood flow occurs (36, 37). It has been cautiously suggested that since, in the dependent position, finger (mainly skin) venous oxygen content increases, flow might be increased (29). The same effect has been found in forearm venous blood (38). Heating the feet and calves resulted in an increased forearm "skin" and an unchanged "muscle" venous oxygen tension, associated with an overall increase in flow (VO Pleth.). Elevation of the legs caused a further increase in flow, no change in skin, and a rise in muscle venous oxygen tension (7).

Another method for the indirect estimation of blood flow is the measurement of the temperature near a small heat source in the tissue. An English translation of an extensive publication on the application of a modified Gibbs thermoelectric needle has appeared (39). A discussion of the comparison of this "calorimeter sound" with the VO Pleth. has also appeared (1). The obvious question concerning the similar appearance of records obtained by the two methods has been asked (40). Since the thermal method is analogous to a "clearance" method, the calibration should be exponential, whereas the VO Pleth. is linear with respect to time. Measurements with the calorimetric probe alone, during the administration of epinephrine and norepinephrine, indicated similar vascular effects from these substances as mentioned above (VO Pleth.) (41). VO Pleth. and calorimeter probe measurements were made on the forearm and calf, and results indicate that muscle blood flow does not increase during indirect heating (4). The calorimetric method has been applied to a comparative estimate of skin and rectal flow (42). A modified Rein "diathermia" flow meter has been used to estimate the effects of phentolamine (regitine) on epinephrine and norepinephrine responses in the legs. It was suggested that they act on the same effector organ (43). A study of the diathermic current indicates that the dissimilar properties of different vessel walls constitute a methodologic variable (44).

Since the proposal by Kety for using Na^{24} clearance as a measure of muscle blood flow, several papers have appeared indicating that marked changes in flow, as determined by other methods, are not associated with significant changes in Na^{24} clearance. A recent study utilizing the perfusion of skinned, isolated hind limbs of rabbits and cats showed a fairly good correlation, within certain limits, between Na^{24} clearance and blood flow. At some "critically" low flow, clearance ceased, suggesting arteriovenous communications. It was also found that at high flow rates clearance did not increase significantly (45). Evidence for the existence of arteriovenous anastomoses (AVA's) in muscle has been adjudged by a reviewer to be inconclusive (14). For discussion of AVA's see also (46) and (47). The possible effects of AVA's in the skin and muscle vex the significance of many of the blood flow measurements in the limb; it seems, however, that many phenomena formerly thought to be due to AVA's are probably due to the functional difference in the circulation of skin and muscle.

The use of impedence plethysmography has led to the conclusion that

distention of the arm with an occlusion cuff causes an increase in forearm flow (said to be muscle) and a reduction in finger blood flow (48, 49, 50).

Cross circulation experiments with dogs have given data suggesting that norepinephine produces a secondary dilation in muscle which is not associated with "pressure" receptor activity nor blocked by atropine (51).

Measurements of blood flow in the limb, using more direct methods, are also of interest. It has been found, by means of a bubble flow meter, that blood flow rates in the knee joint of dogs are relatively high, labile, and vary directly with joint temperature. Epinephrine given intra-arterially causes constriction of vessels. It appears that the joint and skin vasculature behave similarly (52). By measuring the venous outflow of skinned hind limbs of dogs and cats [anesthetized with chloralose (α-D-glucochloralose, chloralosane)] additional evidence has been presented to show the anatomical and functional differentiation of sympathetic inhibition and direct vasodilation as mechanisms for increasing blood flow in muscle (53). A method has been described for estimating flow in the cat's hind limb from pressure changes within the femoral artery following blockage of inflow. It was concluded that flow ceases at a finite arterial pressure, the magnitude of which can be increased by infusions of epinephrine and norepinephrine; "critical closing" was the suggested mechanism (54). If criticism of previous experimental evidence for critical closing is warranted, it would be on the basis that it must be shown that a finite pressure gradient exists across the "closed" vessels. To this author's knowledge such information is lacking in most studies. It remains difficult for this author to conceive of closure of a vessel on the basis of Laplace's equation if the tube wall has a finite thickness. Presumably the vessels implicated in "critical closing" have a sizable wall thickness compared to their radii.

Direct studies on the effects of variations of transmural pressure have shown that when parallel changes in venous and arterial pressures are produced, an increase in pressure levels always results in a decreased resistance in isolated hind limbs of dogs (anesthetized with pentobarbital) (55). Also by the same technique it was found that "homogeneous" perfusion liquids (saline, dextran, plasma) flowed at higher rates but the change with respect to pressure was approximately the same as that of whole blood (56). It may be concluded from this interesting series of experiments that, although the vascular bed is a poor viscosimeter and blood viscosity may be a poor term, there are no evidences of myogenic or local reflex mechanisms tending to maintain a constant or even reduced flow when transluminal pressure is increased. In addition, there was no evidence of "anomolous viscosity" effects. In another series of experiments in which flow was controlled, and pressures were measured in the brachial artery, cephalic vein, and "small" artery and vein of the fore limb of dogs, it was concluded that elevations in pressure in the veins and small vessels resulted in no change in the total resistance, decreased arterial and venous resistance, and an increased small vessel resistance which was abolished by nerve block high in the limb. It was con-

cluded that there are changes in the small vessels that tend to oppose passive stretch but that they are not due to myogenic activity or local reflexes (57).

It appears that with a variety of procedures, methods, species, and anesthetic agents the data of vascular behavior following changes in intraluminal pressure and flow changes in limbs are too variable to permit generalizations or the postulation of any physiological "laws."

The effects of many other variables on limb circulation have been investigated. It has been shown, in the rabbit's isolated hind limb, that the constrictor effects of vasopressin were very sensitive to Mg, Ca, glucose, and oxygen concentrations and to Na: K ratio (58), and that "tone" *per se* was also sensitive to the Na/K ratio, corticoids and oxygen levels in the perfusate (59). The marked variations in skin oxygen tensions that may occur during vasoconstriction and dilation and during respiratory changes have been stressed (34). The introduction of rather large amounts of norepinephrine into dogs caused a marked depletion of potassium and a variable gain of sodium in the wall of the femoral artery (60). After administration of cortisone, by observing injected india ink, it appeared that the vessels of the corium increased in diameter whereas total skin and capillary diameters may have decreased (61).

It has been suggested that the cardiovascular effects of insulin hypoglycemia are attributable to release of epinephrine since ganglioplegic agents were found to attenuate the effects and the associated lactacidemia (62). The opposite conclusion, however, has been reached by others, since hand blood flow (VO Pleth.) increased during insulin hypoglycemia in innervated and sympathectomized limbs (63); but the concern of these workers about sweating seems not to be germane, since many vagal effects are known to follow insulin administration. Comparisons of direct and indirect measurements of arterial pressure during the cold pressor test have appeared (64). Some markedly simplified techniques have been proposed for measuring limb circulation (65, 66, 67). Possibly they may have clinical usefulness.

Modifications of the reflection photoelectric plethysmography technique for estimating blood flow have been reported (68, 69).

Renal Circulation

A long awaited account of experiments and concepts concerned with the differential flow of red corpuscle and plasma within the kidney has appeared. The experiments involved the use of I^{131} HSA and P^{32} labeling of blood components in cats (anesthetized with chloralose). It was estimated that the "normal" intrarenal/renal artery hematocrit ratio is approximately 0.5 and that the ratio varies directly with the renal artery blood hematocrit and inversely with the renal artery blood pressure. Considerations of total blood flow, continuity, and of the probability that the renal artery hematocrit represents that part of the blood which passes through the postulated renal vascular structures, imply average RBC velocities of more than twice the average plasma velocity. Even theoretical "fully developed" laminar flow

and complete centralization of red corpuscles in the flow stream cannot explain such velocities in a single flow path; therefore, the authors have proposed a unique vascular arrangement that further separates plasma and red corpuscles into different long and short pathways through the kidney. These hypothetical unique properties of vascular arrangements within the kidney and shear stresses in flowing blood have been combined into a concept of autoregulation of renal blood flow and proposed as an explanation for certain vexing problems of renal physiology, viz., PAH and iodopyracet extraction and renal oxygen supply (70, 71, 72). Other studies with Cr^{51}-labeled red corpuscles and I^{131} HSA in dogs (anesthetized with pentobarbital) provide confirmatory qualitative data (73). The passage of wax pellets of varied diameters through dogs' renal vasculature produced no evidence of AVA's (74). It was reported that when "venous" pressure was increased in the perfusion of dogs' isolated kidneys the calculated flow resistance increased to a greater degree than when "arterial" pressure was increased. External pressure and infused procaine or potassium cyanide abolished the effect; thus it seems that renal vessels may possess myogenic reactivity to pressure stress (75). Chronic denervation, ganglioplegic, and sympatholytic drugs eliminated the increased "pressure-increased" resistance effect in dogs' perfused kidneys, and the accompanying increase in urine flow suggested involvement of "hormones" (76). Perfusion with 5-hydroxytyromine (serotonin) indicated that large doses are necessary to produce changes in renal blood flow (77). From studies of the effects of ACTH and 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethane (Rhothane, DDD) on renal blood flow and filtration fraction (PAH and inulin) it was concluded that the two inner zones of the adrenal affect renal circulation (78).

Many papers dealing with clinical aspects of renal function have appeared, some of which have more physiological implications than others. An extensive study of a variety of cardiac patients, with and without heart failure, produced no obvious correlations between various circulatory and kidney functions at rest and during recumbent exercise (79). Estimates of renal blood flow, by means of krypton^{85}, and oxygen consumption in anuric renal failure showed average reductions of approximately 75 per cent (80). Other studies are reported that involve renal circulation in such clinical conditions as valvulotomy and mitral disease (81), aortic isthmus stenosis (82, 83), hypertension (84, 85), and chronic anoxia (86).

Coronary Circulation

In some general discussions of current problems related to the coronary circulation, the question whether myocardial systole impedes or augments coronary blood flow and the "efficiency" of the heart has been considered. Comparative measurements of arteriovenous oxygen content of the perfused coronary circulation of open-chest dogs, during asystole produced by vagal stimulation and during rhythmic contractions, indicated that flow increased by an average of about 50 per cent during asystole but that oxygen utiliza-

tion did not change appreciably. It was suggested that the working "efficiency" may be very much higher than usually thought or that something akin to oxygen debt occurs, and similarities between these and the findings in skeletal muscle were pointed out (87, 88). Other workers consider that vagal stimulation causes coronary vasodilation, and the biphasic flow curves obtained at constant perfusion pressure have also suggested additional metabolic effects associated with prolonged vagal stimulation (89). Other studies of the coronary circulation in dogs (anesthetized with pentobarbital) have given evidence suggesting that the heart may function anaerobically or utilize hydrogen acceptors other than oxygen for relatively long periods. These changes are associated with heart rate and cardiac load (90). Infusion of epinephrine (L-adrenaline hydrochloride), L-arterenol hydrochloride and norepinephrine bitartrate into isolated guinea pig hearts were reported to produce dilation; norepinephrine appeared to be most effective. In hearts rendered inactive by potassium chloride the same effects were evident but attenuated (91). In a study of the dilator effects of adenine nucleotides, adenosine, and phosphorylated derivatives in the perfused hearts of open-chested dogs (anesthetized with pentobarbital), studied by means of a rotameter, it was found that adenosine and its monophosphate were approximately equally active and each about a fourth as effective as ADP and ATP (i.e., flow increased to a greater degree than oxygen consumption). With the exception of uridine triphosphate, which was one fourth as effective as ATP, the derivatives of hypoxathine, guanine, cytosine, and uracil lacked measurable dilator effects (92).

It is considered that reflux of opaque media from the atrium into the coronary sinus is abnormal and indicates a breakdown of a normal valve mechanism (93). Studies of the capillary distribution in heart muscle by means of a staining technique have been reported. In the left ventricle one capillary supplies one muscle "fiber" in normal, senile, and hypertrophied hearts; in the right ventricle the same relationships hold, except that the capillary mesh is more dense (94). A cannula and plexiglass window technique has been described for observing and manipulating the cardiac surface through the chest wall (95). During hypotension produced by high spinal anesthesia it was found that coronary blood flow (N_2O method) fell in proportion to arterial blood pressure and that oxygen consumption was reduced without change of the extraction coefficient, implying that myocardial oxygen supply was adequate for the reduced load. The arteriovenous differences in glucose, lactate, and pyruvate were not found to alter during hypotension (96). In view of the controversy about the effects of hyperthyroidism on myocardial circulation, additional studies of thyrotoxic patients have been made. Coronary blood flow (N_2O method), arteriocoronary sinus oxygen content, cardiac output (Fick), and direct arterial pressure measurements have produced evidence that the general hypermetabolic state includes the myocardium and that cardiac oxygen consumption returns to normal following treatment (97). A study designed to gain additional information on

certain pharmacological coronary vasodilators has indicated that, of those studied, only pentaerythritol tetranitrate (Peritrate) is worthy of the name "long acting" (98). Experiments concerned with the effects of aortico-coronary sinus anastomosis have been reported (99).

Cerebral Circulation

The N_2O method was used to determine the minimal changes in arterial CO_2 tension associated with cerebral vasodilation in man. Breathing $3\frac{1}{2}$ per cent CO_2 caused a 10 per cent change in apparent flow. With constant cerebral metabolism it was calculated that a cerebral blood flow (CBF) reduction of approximately 30 per cent would be required to raise end capillary pCO_2 to dilator threshold levels (100). It is comforting to learn that mental arithmetic does not require an increased CBF or oxygen uptake nor is it associated with CO_2, pH, or hemoglobin changes (101). Another study leaves in doubt the hypotheses that sleep is induced by cerebral ischemia or anoxemia, depressed cerebral metabolism or generalized narcosis, since during sleep a slight increase in CBF, a slight decrease in "resistance" and no change in cerebral oxygen consumption or arterial oxygen content was found (102). Utilizing a method of heat exchange (modified Gibbs), studies of the effects of certain drugs (theophylline and derivatives) were made on apparent blood flow and pressure; all lowered apparent CBF except Kgg[168] (water soluble theophylline derivative substituted in 8-position; its hydrochloride is twice the molecular weight of theophylline), histamine, and papaverine (103). Angiographic studies showed that in some patients Paveril may increase CBF (104).

Since the N_2O method is inadequate for measuring rapid changes in CBF, the use of radioactive krypton (105) and T-1824 (106) have been investigated. Each was reported to be in good agreement with the N_2O method.

It is claimed that volume flutuations in CBF and cerebrospinal fluid can be measured by impedence plethysmography (107).

Splanchnic Circulation

In a stimulating conference on the splanchnic circulation it was emphasized that oxygen consumption remains quite constant in patients with congestive heart failure, moderate hemorrhage and severe anemia, yet in the first two conditions splanchnic blood flow (Sp.BF), measured by the BSP method, is reduced and in anemia it is increased. It is stated that in congestive failure resistance is up since arterial pressure was normal (no estimates of venous pressures were given); in severe anemia the hepatic venous blood oxygen content may be as low as one per cent; in hyperthyroidism the Sp.BF is normal but the arteriovenous oxygen difference is increased; infusions of amino acids, which increase some metabolic load, also increase Sp. oxygen consumption without changes in flow; in hemorrhage the percentage extraction of BSP is increased (108). Using a closed system for perfusing the isolated dog's liver it has been found that the BSP extracted from hepatic

artery blood is almost 2.5 times greater than that from the portal vein. Norepinephrine and epinephrine reduced hepatic artery BSP extraction at equivalent flows. It was concluded that measurements of BSP clearance may not reflect changes in portal blood flow (PBF) if hepatic artery flow does not alter (109).

Hepatic "wedge" pressures, obtained by passing a catheter through the hepatic vein until it becomes lodged, are reported to have a "normal" value of approximately 5 mm. Hg and are said to represent portal venous pressure (PBP); however, there is some gradient which appears to be reversed with infusions of epinephrine (108, 110). It is likely that the proposed significance of these pressures will be subject to the same criticisms as those of pulmonary wedge pressures. It has even been suggested that portal venous pressure changes brought about by ACh need not be explained by circulatory changes (111) and that anesthesia changes the portal pressure (108).

By means of transcutaneous needle punctures pressure (112) and temperature (113) measurements have been made in the liver parenchyma. By the same means, pressure in, and circulation times to the tongue from the splenic parenchyma have been determined (114). There are many indications that the intrahepatic communications of the portal and hepatic artery vasculature are not simple. Additional evidence that areas of the liver may, at times, be isolated from the PBF has been obtained by means of thorium dioxide suspension (Thorotrast) injections into the portal veins of rabbits (115). For a discussion of sinusoid sphincter action where the reservoir action of the liver is emphasized, see the reference (116). It has been reported that the liver can survive if the hepatic artery and portal vein are ligated and that the nutrition is sustained by flow from branches of the phrenic artery (117, 118). Further experiments indicate that these communications are via the intrahepatic branches of the hepatic artery but not the portal vein (119). A consideration of intrahepatic vascular anatomy has been published (120).

An interesting and detailed study of certain of the relationships between pressure and flow in the portal vein, hepatic artery, and intrahepatic vasculature has appeared. In splenectomized dogs (anesthetized with morphine-chloralose) perfusion of the portal vein and hepatic artery while measuring flow (rotameter) and pressure indicates that incremental changes in pressure produce an increase in flow through the portal system of 38 times that of the hepatic artery. Pressure-flow relationships were found to be complex with decreasing resistance at increasing pressure differences in some conditions, and the reverse in others, depending upon the state of "surgical shock," degree of anoxia (produced by nitrogen breathing) and epinephrine perfusion. It was found that flow ceased at variable finite pressure levels. Differences in curves were obtained with increasing and decreasing flow and pressure rates, innervation, and denervation. Detailed analyses of the pressure-flow curves were presented (121).

The splanchnic vasculature, like others, lies within different organs and

tissues whose mechanical and metabolic activities are different and variable. Since the innervation of the vessels and these tissues are somewhat harmonic, the interrelationships of effects are difficult to separate. There are grossly three splanchnic vascular pathways to the liver: hepatic artery, splenic artery-portal vein, and mesenteric vessels-portal vein. An attempt to establish a frequency distribution of flow through these beds has been made (122). Much remains to be learned about the "vasodepression" that accompanies hepatic ischemia. Experiments have been reported on splenectomized dogs (anesthetized with pentobarbital) in which PBF (rotameter), systemic arterial pressure, PBP, and inferior vena caval pressure measurements were associated with hepatic ischemia (shunting hepatic blood flow) of 2 hrs. duration. During ischemia arterial pressure and PBF fell slightly; after reestablishing liver flow, arterial pressure fell markedly, accompanied by a transient increase and then a decrease of portal and mesenteric flow "resistance" and marked increase in PBP. The considered opinion was that the depressor effect, lasting about 5 min., is humoral and possible substances are listed (123). Using the same preparation to investigate some of the relationships between arterial pressure and severe hypercapnia (breathing 5 to 16 per cent CO_2 and 21 per cent O_2), it was found that there was an increased PBF and PBP, accompanied by a decreased arterial pressure. It was suggested that at these levels CO_2 may cause dilation of mesenteric vessels (124). In a study of the functions of the splanchnic nerve supply to the mesenteric vasculature, the flow and pressure in the mesenteric artery in response to stimulation of this nerve and intra-arterial injections of epinephrine and norepinephrine before and after adrenergic blockade were measured. Results of a study of the functions of the splanchnic nerve support the conclusion that it affects only mesenteric constrictor activity (probably via norepinephrine) and release of adrenal medullary secretion. No evidence for active (cholinergic) vasodilation was found (125). Hepatic vein flow (Gaddum meter), liver volume (plethysmograph), and portal perfusion data from dogs suggest that epinephrine and norepinephrine cause constriction of both hepatic arterial and portal vessels but have no effect on the hepatic vein, and further, that acetylcholine and histamine dilate hepatic vessels (if they were previously constricted) and constrict the portal and hepatic veins (126). It has been reported that considerably greater doses of norepinephrine and epinephrine and acetylcholine are required to produce similar arterial pressure effects when injected into the portal vein or hepatic artery than when injected into the saphenous vein. It was estimated that the liver is capable of inactivating up to 5 mg. epinephrine per hr. and 180 mg. acetylcholine per hr. when injected via hepatic artery, and 250 mg. acetylcholine per hr. via portal vein. It is also stated that the liver stores, rather than inactivates, histamine (127). Studies on cats (anesthetized with chloralose and urethane) using protoveratrine and 5-hydroxytrypatimine (serotonin) and the concept that they act by stimulating "coronary chemoreceptors" have led to the suggestion that splanchnic nerve activity is inversely proportional

to chemoreceptor activity and directly proportional to "pressoreceptor" activity (128).

The problem of splanchnic circulation and hemorrhage continues to excite interest (108). In dogs (anesthetized with pentobarbital) sustaining acute hemorrhage, Sp.BF (BSP method) decreases in proportion to cardiac output but returns to normal more rapidly during recovery; splanchnic "resistance" remains normal, while systemic "resistance" increases; Sp.BV (using I^{131} HSA) is reduced by 50 per cent. During severe and prolonged hemorrhage Sp.BF remains low, liver function deteriorates and Sp.BV is reduced. The reduced Sp.BV in both acute and prolonged hemorrhage occurs with and without the spleen. It is concluded that the splanchnic vasculature does not contribute to the overall increase in resistance but does function as a blood reservoir (129). Confirmation of the changes in Sp.BF in hemorrhage is given by other studies of cardiac output (rose bengal dye dilution) and Sp.BF (same dye; clearance) in dogs (anesthetized with pentobarbital). Of six dogs studied, Sp.BF rose in 4 and fell in 2. In one dog, Sp.BF was estimated as 75 per cent of the cardiac output. This work suggests that Sp.BF continues at the expense of the body. These studies do not include estimates of Sp.BV (130). In more recent studies on dogs' (anesthetized with pentobarbital) blood flow (bubble flow meter and rotameter) in mesenteric and hepatic arteries was compared during hemorrhage and infusion. Relationships of these flows and PBP were found to be complex and reciprocal under certain conditions (131).

The effect of hydralazine (L-hydrazinopthalazine, Apresoline) on Sp. circulation has been further studied; it was found that the Sp.BF almost doubled, and it was concluded that this contributed to the fall in arterial pressure (132). The cerebral cortex of cats (anesthetized with ether, chloralose, urethane, pentobarbital, or thiopental) was stimulated before and after splenectomy. The rise in arterial pressure caused by stimulating two areas of the ventral and dorsal surface of the frontal lobe, was attenuated by splenectomy; however, the rise caused by stimulating the orbital gyrus was unaffected (133).

Pulmonary Circulation

The major difficulty besetting workers in this field is that of assessing the factors that relate blood pressure and flow because: pressure differences are small and hard to measure; changes in the function of the heart and systemic circulation are quickly reflected in the pulmonary system; mechanical changes in the lung tissue affect its vasculature; the distribution of chemical (gas) changes in the lung are difficult to determine; and the effects of the bronchiolar circulation are variable. Whether or not the right ventricle plays an important role in moving blood from the right atrium into the pulmonary artery has been debated. This has been reinvestigated by experiments that by-passed the right ventricle through aortic grafts, and the conclusion was that the right ventricle is necessary for adequate flow (134). From an-

other study it was concluded that, in dogs, the pressures in the peripheral veins, atria and pulmonary artery rise and fall in unison during peripheral venous infusion and withdrawal of blood (135).

It has been concluded, from experiments with complex pulmonary systemic vascular isolation and perfusion techniques, that sympathetic nerve activity results in pulmonary vascular constriction (136) and that epinephrine and norepinephrine cause such constriction by direct action (137). It has also been suggested that the increase in pulmonary blood volume estimated by the Newman dye curve method following the infusion of L-arterenol in splenectomized dogs is attributable to a shift of blood from the systemic venins (138). Confirmatory evidence that pulmonary arterial pressure (Pu.AP) increases during exercise in man (139) and dog (140) has been presented.

The effects of diffuse obstruction of small pulmonary vessels have been investigated further. Injections of lycopodium spores into dogs were reported to produce pulmonary hypertension independently of changes in "central blood volume" and of cardiac output, and not proportionately related to anoxia. It was concluded that the effect was mechanical (141), although it is difficult to accept the finding that "central blood volume" does not change if Pu.AP increases. In intact dogs, heart-head-lung and heart-lung preparations, barium sulfate injections indicated that the pulmonary hypertension was associated with sympathetic nervous influences on the vasculature of the lungs (142). Evidence that this hypertension is the result of both mechanical obstruction and neuroreflex effects was found following the injections of glass beads into dogs. It was also concluded that part of the peripheral anoxia was due to opening of pulmonary arteriovenous shunts (143). By relating the passage of wax beads of various diameters in dogs' isolated perfused lungs, it was concluded that there were no apparent A-V shunts (144). Utilizing a pO_2 measuring electrode, the technique of Riley and Lilienthal for estimating A-V shunts was extended, and it was concluded that normally such shunts account for less than 4 per cent of the total pulmonary flow (145); this agrees with previous estimates.

The cause of the pulmonary hypertension that results from breathing low oxygen mixtures continues to arouse interest. The dye dilution method has been used to measure cardiac output because of possible difficulties with the Fick during anoxia, and in cats it was estimated that the hypertension was due to increased pulmonary resistance whereas in the dog it was due primarily to increased flow (146). Interesting studies of the differential flow through each lung in man by means of bronchospirometry have been reported by two groups. In a summary of preliminary findings one group has reported that unilateral hypoxia does not cause an increased resistance in or a shifting of blood flow from the hypoxic lung, whereas bilateral hypoxia causes an increased Pu.AP due to increased flow (147). The other group has estimated that there is a shift of blood flow from the hypoxic lung (148). For further discussion of this problem see the bibliography (149).

A third group, applying somewhat the same technique in animals, has estimated that there is an increased vascular resistance in the hypoxic lung (150).

With isolated blood-perfused cat lungs it was found that increased left atrial pressure (LAP) (to 15 cm. H_2O) caused a marked decrease in pulmonary "resistance" (Pu.PA-LAP/flow), and a further increase to 35 cm. H_2O caused a further increase in Pu.AP with little further decrease in resistance. Pulmonary volume increased approximately linearly with LAP. Section of cervical sympathetics and stellate ganglion and atropinization did not alter the results (151). It has been reported that LAP changes cause similar changes in pulmonary capillary pressure but not in pulmonary "arteriolar" pressure changes (152).

The depressor effects of systemic "baroreceptor" stimulation on the circulation in the lungs have been studied in open chest dogs (anesthetized by morphine pentobarbital or chloralose) and it was concluded that they were in part caused by changes in the systemic and bronchial circulation as well as by changes in lung mechanics (153). An ingenious method of estimating pulmonary capillary blood flow by measuring the pressure change in a whole body plethysmograph after inspiring N_2O has indicated that flow in these capillaries is pulsatile; however, the total flow values reported are lower than the usual "standards" (154). In an interesting study three methods for estimating pulmonary blood volume and hematocrit were compared; although each method gave different values, they all indicated a lower pulmonary than "large vessel" hematocrit (155). Since intrapleural pressure is often estimated by measurements of intraesophageal pressure, it is interesting that one group found a poor correlation between the two in humans in the recumbent position (156). It has since been reported that the relationship between the two are better in the sitting position (157). Results of catheterization studies in patients with pulmonary stenosis have been interpreted to mean that pulmonary artery dilation in this condition may be due in the arteries to abnormalities rather than "hydraulic" effects (158). The time and relative magnitude of development of collateral pulmonary circulation after ligation of the left pulmonary artery have been described (159).

Capillaries and Lymph

It has frequently been observed that, after a volume of liquid containing particles of certain sizes is introduced into the vascular system, a proportion of the volume and particles soon leave the circulation. It has been suggested that the amount that makes its exit is related to the degree of vascular "overdistention" produced by the infused volume. Presumably this loss occurs across the capillaries and into the lymph. In a series of papers dealing with this and related problems, the rate of disappearance from the blood of various infused substances, e.g., tagged (I^{131}) albumin and dextran fractions, and their rate of appearance in the various lymph channels of dogs have been measured. Some of the interesting conclusions suggested are:

that there is continuous leakage of protein and a large range of sizes of dextran molecules (mol. wt. 35 to 400 thousand); that the molecular sizes and their apparent rate of movement vary in different organs; that when the vasculature is "distended" by large infusion, the size and number of particles passing through the capillaries increase; that of the amount of plasma passing into the vasculature after hemorrhage, 50 per cent comes from the extravascular space within 24 hrs.; that the measurement of plasma volume by the tagged albumin or dextran (mol. wt. above 35,000) dilution methods are reliable (160, 161, 162, 163). In another study of rats and rabbits it was found that the protein concentration in lymph from liver and intestine varied inversely with the rate of lymph flow and that the protein concentration and the rate of exchange of (I^{131}) tagged albumin between plasma and lymph is rapid in liver, intermediate in intestine, and slow in skeletal muscle (164). A study of the rate of disappearance of PAH from the circulation and considerations of some factors of which such curves are functions have led to the provocative suggestion that as much as 75 per cent of the filterable components of the cardiac output circulates, in bulk, extravascularly and, further, that filtration dominates transcapillary exchange (165, 166). It would seem that the mechanism which dominates the transcapillary transfer of a substance should be dependent upon the diffusion coefficient of the substance, i.e., filtration predominating in exchange of large molecules and diffusion in the case of highly diffusible molecules. A study of the disappearance of various substances from the isolated perfused hind limb of cats has suggested that, theoretically, the effects may be treated as if there were two parallel exchange regions, one perfused well, the other perfused poorly (167). It is possible, however, that there are other mechanisms to explain the complexity of such disappearance curves. It does not seem possible to this author that the number of parameters which determine a composite disappearance curve can be deduced from the disappearance curve alone.

It has been reported that three isotopes of water can be used interchangeably in the study of physical mechanisms of water transport (168). D_2O has been used to study water exchange between intestinal contents and blood, and it was concluded that two of the possible number of limiting variables are low mucosal capillary "permittivity" to water and A-V shunts in the intestinal circulation (169).

There have been many interesting techniques developed and extended for the investigation of capillary, AVA and related small vessel behavior by microscopic observation of the rabbit ear (170), liver (171), bulbar conjunctiva (172), and retina (173). Anatomists are becoming increasingly interested in the "dynamic" anatomy of the circulatory system, and it is apparent that they have much to offer to physiology (46). There is no doubt that the overlap of interests of "circulatory physiologists" and "circulatory anatomists" is considerable, and each can learn much from the other. The difficulty is in communication, the lack of overlap in modes of communication, terminology and the reading habits of the two groups leaves much to be desired. The same

thing can be said about the relationship between neurophysiology and circulatory physiology.

This author is inclined to agree with one of his predecessors (174) that the term capillary permeability is often misused (175). Studies have been made of ptechiae counts in the skin in exercising athletes (176), and in other forms of "stress" (177, 178).

Some relationships between sodium and water retention in patients with heart disease who tend to develop edema and increased venous pressure have interested workers for many years. It is generally assumed that the cause of edema and water and sodium retention in cardiac patients may not be increased venous pressure *per se;* certainly it is not the only factor. In a recent study of electroyte balance in such patients, evidence has accrued in support of the concept that such tissue fluid retention does not initially depend upon an increased venous pressure (179). It has been suggested that the fluid retention associated with administration of ACTH and cortisone differs from that found in congestive failure in that with the former cardiac function does not appear affected (180). It has been estimated that transcapillary movement of cholesterol is related to the blood levels and general transcapillary fluid movement (181). Although it is not claimed that observations of intradermal injections of riboflavin is a messure of lymph flow in the area, qualitative differences in the behavior of lymph vessels in normal and lymphedematous patients were found (182).

Blood Volume

This subject, as an entity, is adequately covered in another section of this volume, and references to blood volume have been linked with other subjects in this section.

A matter that has excited much interest concerns differences in the ratio of plasma to red corpuscular volumes in various regions of the vasculature. Despite these regional variations in hematocrit values, it has been claimed that under "normal" circumstances, the "total body hematocrit" bears a constant relationship to the venous blood hematocrit. Studies have indicated that in conditions of hemorrhage, chronic anemia, dehydration, postoperative shock (160, 183), pregnancy and the puerperium (184) such an assumption may not be valid. It has also been pointed out that in dogs the effect of blood sampling and the presence of the spleen may cause variations of hematocrit measured from one sample to another in the same animal (185).

It has been reported that, because of its adsorbtion on glassware, the use of Cr^{51} as a blood volume indicator is subject to a constant source of error, which can be corrected by use of a chromium carrier (186). One group has estimated (Cr^{51} tagged red corpuscles) that body fat contains approximately two-thirds as much blood as lean tissue (187).

An interesting method has been described for estimating the blood volume in the limb by means of an analysis of gamma-activity following injections of I^{131} HSA. It was estimated that in the recumbent position 60 per cent of the

blood volume is in the musculoskeletal system (188). Blood volume measurements utilizing P^{32} tagged red corpuscles were investigated with respect to nutritional status. The relationships depended upon the treatment of data, and the pitfalls in calculating relative values were emphasized (189). The P^{32} method was also applied to patients with congestive heart failure and it was again estimated that the blood volume was increased in the decompensated state (190).

Although changes were not large, it was concluded that blood volume varied in the opposite direction to venous and arterial pressure (Cr^{51} and T-1824 methods) during general anesthesia in man (191). It has been estimated that the cardiac output (T-1824 dilution curve method) increased in dogs with thiopental analgesia and decreased when cyclopropane was given (192).

General Considerations of Vasoactive Substances

One of the originators of the rat mesoappendix test has applied the technique to other rat vascular beds and concluded that each may behave differently (193). The cheek pouch of the hamster has been investigated as a test area, and it was suggested that the "dilator" effect of VDM might be direct rather than by modulation of epinephrine activity (194). The effects of Fe^{++} in attenuating the constrictor response to Adrenalin [a commercial mixture of epinephrine and norepinephrine] and to epinephrine and norepinephrine separately in the rat mesocecum has been confirmed and participation of a direct effect, an epinephrine inactivating mechanism or both, were suggested (195). Interesting observations on the behavior of bat wing vessels have been reported. Vessel outside diameters were measured following nerve section and degeneration. Epinephrine produced an increased constrictor response, if introduced intravenously but not if applied topically. It was suggested that hypersensitivity may be associated with altered vessel or effector cell permeability to epinephrine, and we are reminded that topically applied substances must permeate several tissue layers to reach these cells. The observation that "arterioles" do not take part in these responses is also of interest (196). Another group found the effects of vasopressin, epinephrine, norepinephrine, phenylephrine hydrochloride (Neosynephrine), angiotonin, and serotonin on the rat mesoappendix when given intravenously to be greater and more reproducible than topical applications (197). The depressor effect of potassium depletion in the rat was found not to affect the mesoappendix response to epinephrine (198).

The opinions of von Euler on the relative efficacy of epinephrine and norepinephrine in the treatment of "hypotensive states and shock" have been summarized, and it was concluded that norepinephrine is the better substance and, indeed, that epinephrine may have undesirable effects (199). The urinary excretion of these substances has often been used to monitor their rate of release in the body. Going from the recumbent to the upright position causes a proportional increase of both, but the magnitude of the urinary

norepinephrine is about triple that of epinephrine (200). It has been suggested that a new unidentified substance, found in urine, may play a role in hypertension (201). The role of monoamine oxidase in norepinephrine metabolism has been further investigated (202). The relationship between increased thyroid activity and the apparent increased vascular effects of epinephrine and norepinephrine has been investigated and was found difficult to evaluate (203). Dogs with intact ovaries and in estrus showed a greater increase in arterial pressure than males, metestrus females, or oöphorectomized dogs following injection of epinephrine (204). It has been reported that hypertension can be produced in rats by cortisone only when there is a combined effect of renal ligature, potassium depletion, and adrenalectomy (205).

In rats with reduced renal mass, the evolution of hypertension is altered by administration of gonadotropin; however, the effect is different in males and females (206). In similar animals thyrotropin, presumably by stimulating thyroid activity, increases the arterial pressure response (207). The relationships of kidney growth hormone (renotrophin) in these animals is also discussed (208, 209).

The effects of "substance P" on the cardiovascular system were found not to be very exciting (210). It has been shown that the cardiovascular responses to 5-hydroxytyramine (serotonin) in human and dog hypertensives, normotensive dogs, and cats were all different and that these responses were augmented by the administration of a ganglion stimulating agent (211). Other reports have been made on the varied effects of serotonin (212 to 215). Careful cephalic-systemic perfusion experiments have indicated that "cerebrotonin" has not been adequately characterized as an entity (216).

Afferent Systems in Reflex Regulation

In the afferent system mechanical, chemical, and perhaps thermal energy is transduced into electrical impulses, but little is known of the fundamental couplings.

Mechanoreceptors.—Mechanoreceptors are too often called pressure receptors. Receptor "output" is a function of its sensitivity to motion,[6] which is a function of its "stiffness,"[7] its coupling to vessel wall structures and to vessel wall motion.[6] The last is a function of vessel wall stiffness and pressure stress (and their time derivatives). Thus, pressure and receptor output are only indirectly related. The effector system is essentially in the reverse order of the receptor system, viz., from neuroactivity through vessel wall properties to blood pressure. Since many of the substances used to study receptor behavior affect both afferent and efferent systems in more than one parameter and are the same substances affecting physiological "regulation," many experimental and conceptual paradoxes ensue.

Although anesthetic effects are difficult to quantitate, there is little

[6] More precisely; displacement and its derivatives, velocity and acceleration.
[7] See "Hemodynamics."

doubt that they have profound effects on many physiological studies. It has been re-emphasized that chloralose accentuates reflex behavior (217), as many previous studies have done for other anesthetic agents. Another study of the effect of volatile agents on the relationships of peak systolic arterial pressure and single afferent fiber activity has been reported. Though findings are difficult to evaluate quantitatively and the arterial pressure records are poorly reproduced, it appears that ether and chloroform increase, at least initially, the afferent activity at equivalent pressures, whereas cyclopropane does not (218). It has been reported that intravenous surgical anesthetic doses of thiopental cause a marked fall in cardiac output and an increase in "total peripheral resistance" (219).

Epinephrine, norepinephrine and, posterior pituitary extract as well as other substances added to otherwise apparently inert fluid bathing isolated strips of carotid sinus wall have again been shown to cause contraction of the smooth muscle (220). Conflicting opinions have been expressed as to whether or not, in the intact animal, the arterial pressure lowering effect of norepinephrine applied to the carotid sinus wall is caused by increased displacement of the wall related to blood pressure changes or by changes in the intramural muscle tension acting directly on the receptors. It has been reported that topical application produces depressor effects in the absence of intraluminal pressure (221). It seems, however, that such evidence does not preclude the effectiveness of pressure stress. In a series of papers (222, 223, 217) it has been emphasized that "baroreceptor" reflexes are unable to modify the arterial pressure reponses to epinephrine, norepinephrine and histamine. This is not surprising, and the reasons are probably associated with the relationships noted above. The results of studies in animal preparations designed to reduce the interrelationships of afferent and efferent effects of vasoactive substances have been summarized. The specific findings are worth reading; the general conclusions are that the afferent "baroreceptor" activity is amplified by morepinephrine, epinephrine and hypertensin (angiotonin) but that the effects of vasopressin are difficult to evaluate (224). There seems to be a return to the earlier opinion that the mechanoreceptor system is related to the genesis of hypertension. It is now recognized, however, that the parameters are more complex than was previously thought (225). It has been emphasized, in chronic denervation experiments, that the effects of postdenervation hypersensitivity of smooth muscle may affect the walls of all vessels, including these containing receptors (226). Interesting studies of the carotid sinus and aortic nerves indicate that there are, in addition to the known medullated A fibers, small nonmedullated C fibers whose stimulation produces marked depressor responses. It is believed that they are associated with baroreceptor activity (227 to 230).

Another complication is the probability that effective mechanoreceptors are widely scattered throughout the vascular system; thus, elimination of the carotid sinus and aortic "buffer" nerves may not eliminate all afferent "information" transmitted to the central nervous system. This reviewer is im-

pressed by the lack of effectiveness in buffering arterial pressure changes in low spinal anesthesia (231). Recent histological investigations of newly found receptor areas in the common carotid arteries have been described (232). Although no results were reported, an interesting method for estimating the mechanical responses of the Pacinian corpuscles to displacement and velocity has appeared (233). So-called vascular volume receptors are probably in some way analogous to the so-called pressure receptors. It has been concluded that the thoracic visceral "stretch" receptors are responsible for "homeostatic" renal responses in the left atrium or terminal pulmonary veins (234).

Chemoreceptors.—Chemoreceptor mechanisms are even more elusive than those of mechanoreceptors because there are so many more kinds of chemical "stress." It is also possible that each may respond to other forms of energy. A report on the depressor effect of topical application of protoveratrine to the carotid sinus "baroreceptor" area has been published (235). Studies of carotid sinus nerve activity from the cat's carotid glomus suggest a greater sensitivity to changes in pO_2 than previous evidence would indicate (236). Rabbit's ears isolated, except for the nerves, from the rabbit are thought to possess chemoreceptors sensitive to epinephrine, acetylcholine and nicotine that are capable of inducing, in the animal, reflex cardiovascular and respiratory responses (237). Studies of the chemoreceptor stimulating action of 5-hydroxytryptamine (serotonin) have been described (238). Preliminary evidence has been reported for the existence of pulmonary chemoreceptors in rats (239).

Central Nervous System in Reflex Regulation

One must agree with the Swedish reviewers (14, 240) that many investigations of relationships of the central nervous system to the cardiovascular system utilize only arterial pressure as a measure of cardiovascular function. These reviewers also note the paucity of information concerning the cortical and hypothalamic influences on the vasomotor system.

Spinal cord and medulla.—It is concluded that neurons in lateral horns may exhibit slight independent activity depending upon the "local environment" and that, in spinal animals, skin pain and cold may elicit a segmental constriction of mesenteric flow and an inhibition of constriction with warmth (14). Foot blood flow (VO Pleth.) in patients with complete cord lesions from, C5 down were studied. Placing the arms in hot water (40 to 44°C.) caused increased flow if lesions were below T10 to 11 (241). Spinal dog preparations have indicated that the postspinal hypotension and recovery depends upon the activity of the vagus nerve (242).

Medulla oblongata.—Evidence to date indicates that this region is primarily responsible for the sympathetic "vasoconstrictor tone" and that here most of the peripheral afferents and higher centers have their principal effect. The same reviewer concludes that no strong evidence exists that there are descending "inhibitory" fibers (14), and it has been suggested that the term vasodilator center for this area is unwarranted (240). Further studies

of the localization of the "depressor area" in the rabbit were presented (243). The direct action of epinephrine in the diencephalon and reticular formation has been investigated (244). A study of the effects of receptor stimulation on the EEG was reported (245).

Mesencephalon.—An excellent publication has appeared of work on cats [anesthetized diallylbarbituric acid (Dial)] of the effects on venous outflow from skin, skeletal muscle (leg), and intestine as a result of stimulating various areas of the mesencephalon, hypothalamus, and medulla (240). It was concluded that the mesencephalon is the most caudal intracerebral relay station of the sympathetic (cholinergic) vasodilator system [most likely pathway: cortex—internal capsule—hypothalamus (relay station)—mesencephalon—medulla—spinal medulla (relay to preganglionic neurons)]. Stimulation of these areas in the mesencephalon caused vasodilation in muscle vessels with coincident constriction in skin and intestine. The vasodilator fibers do not appear to make functional connections with the sympathetic vasomotor center of the medulla. It is suggested that the anatomy and integrative physiological functions of these two systems are separate and distinct [cf. also (53)].

Hypothalamus.—Current opinion holds (14) that the major pressor area is in the posterior, with the "heat loss center" in the anterior region (chiefly affecting skin). Injections of procaine and thiopental into the posterior region of cats produce a depressor response (246). Similar injections of acetylcholine and histamine increase peripheral sympathetic discharge (247).

Cortex.—The production of hypertension in hemidecorticate rats has been further investigated. Increased arterial pressure developed in approximately one month and lasted no more than two. Adrenalectomy and sympatholytic drugs lowered the pressure. It was concluded that the transitory effect was due to removal of a cortical modulating effect on lower structures (248). Thoracic sympathectomy (T5 to 12) and adrenalectomy attenuates the increased arterial pressure response following stimulation of the motor and premotor regions in dogs (249). It is claimed that alterations in blood flow and arterial pressure can be brought about by conditioned reflexes (250, 251, 252).

Efferent Systems and Reflex Responses

Many of these aspects have already been mentioned. One aspect concerns the various opinions about the existence of a third efferent sympathetic link, peripheral nerve ganglia, or plexuses (14, 253). In a detailed study of the cardiovascular effects of intravenous injections of hexamethonium it was found that cardiac output (Fick), arterial pressure, renal blood flow (flow meter), and urine production fell; the depressor effects of vagal stimulation were markedly attenuated; the action potentials from lung "stretch" receptors were not affected (254). It has been reported that, in humans, hexamethonium blocks the increase in cardiac output but not the increase in renal blood flow produced by hydralazine (255). A new longer acting

"ganglioplegic" drug has been described (256). It has been suggested that the effects of tetraethylammonium are primarily due to the "adrenerg-amine-mobilization" from the adrenal (257). There are numerous publications on the effects of ganglion blocking and "tranquilizing" drugs in hypertension; however, their review is excluded with the excuse that they are primarily of clinical interest. We have again been warned against accepting, uncritically, the existence of physiological mechanisms based upon responses to ganglion blocking agents (14).

Cross perfusion studies of dogs (anesthetized by chloralose) have re-emphasized the augmented synaptic and neuroadrenal glandular transmission with epinephrine in low doses and the reverse in higher doses. It is suggested that these effects may be due to changes in the metabolism of neurons of chromaffin cells. It is also suggested that this "dual" action may constitute a self-regulating mechanism (258). That the vasomotor supply to the adrenal is capable of reducing the flow therein to one-tenth of doubling it has been reported (259). Comparison of adrenalectomized dogs (anesthetized by small doses of pentobarbital) and "normal" dogs (anesthetized by morphine and pentobarbital) in their response to epinephrine, norepinephrine, and nicotine suggested that the hypotension of adrenal crisis is not due to "asthenia" of the arterioles (260). It has been re-emphasized that the adrenal medulla's secretion of vasoactive substances probably does not play a large role in cardiovascular regulation except through their metabolic effects (14). A brief review of certain aspects of reflex regulation of the circulation has appeared (261). It is interesting that in dogs (anesthetized by chloralose or morphine, diallylbarbituric acid-urethane-pentobarbital or morphine-barbital) the hypertension following section of the carotid sinus and mid-cervical vagosympathetic nerves was not accompanied by a significant change in cardiac output (Fick). It is also interesting that the hematocrit increased considerably. From the data given, it is difficult to relate individual responses to the anesthesia used (262).

Studies on dogs (anesthetized by pentobarbital) and the results of previous work have motivated the proposal of a schema to explain the arterial hypertension that accompanies increased intracranial pressure. It includes "pressoreceptors" (probably in the medulla), activation of the vasomotor center to effect a neurogenic vasoconstriction, increased arterial blood volume, and the release of "graded" amounts of a humoral pressor material (263). In another publication essentially the same conclusions are reached; after vagal section or decerebration or both, the pressor response is increased, while cordectomy at C7 or adrenalectomy or both, causes an attenuation of the response. Sympatholytic drugs may abolish the response (264).

It has been reported that antidromic vasodilation can be produced in the isolated rabbit ear with perfusates other than plasma by stimulating the great auricular nerve (265). It has also been suggested that reactive vasodilation in the same preparation may be due to myogenic reactivity independent of

neural or humoral activity (266). It is, apparently, possible to separate the effective innervation for secretory and vascular behavior in the submaxillary gland of the cat with sympatholytic agents (267, 268, 269).

Hemodynamics

The word "hemodynamics" probably brings a somewhat different aspect of cardiovascular physiology to the mind of each individual according to his experience and interests. To everyone, however, the word should imply that changes in the position(s) of some vascular element(s) are occurring in such a manner that time is an important variable. The word implies consideration of the interplay of forces tending to produce and prevent motion. In reality, only very simplified theoretical manifestations of "force" are dealt with; friction or viscosity, mass or inertia, elasticity, and structure or geometry. The problems facing the physiologist become more apparent when it is noted that accomplished theoretical fluid mechanicists and mathematicians have been able to develop solvable equations only for relatively simple "non-living" fluid-mechanical situations: a single straight tube with linear, thin, viscoelastic walls containing an ideal viscous liquid that possesses mass and to which is applied a simple periodic stress (force) of small magnitude and long wavelength. Indeed, regardless of how elaborate such derivations become, they have as their basis the classical Navier-Stokes equations, which relate velocity and pressure in liquids in a very special way. In spite of the fact that hemodynamics is more complex than such simplified fluid mechanics, these derivations are very enlightening. They have, for example, indicated that in such a situation the velocity and damping of a traveling pressure wave is dependent upon the frequency of the wave. The use of the velocity of the arterial pressure pulse as a measure of arterial elasticity then becomes questionable on purely theoretical grounds because it is evident that vessel walls are viscoelastic, blood possesses finite density, and the involved wave frequencies are complex and variable. A superb analysis of oscillatory pressure and flow in such a simple hypothetical tube, as mentioned above, has recently appeared; it relates the additional effects of wall mass and fluid viscosity to the wave velocity and damping (270). A useful technique has been developed for subjecting isolated strips of blood vessels to oscillatory motion in order to evaluate the wall friction of such strips.[8] It has been found that even strips obtained from the thoracic aorta possess considerable nonlinear damping properties which are believed to be due to uncoiling of molecules but which are, nevertheless, analogous to friction or viscosity in terms of mechanical energy dissipation (272). This loss of mechanical energy during stretch is implied in the hysteresis loops that have often been obtained when vessel strips are rapidly stretched and relaxed. In a recent paper it was

[8] A similar type of study has been made independently and was reported earlier (271).

suggested that the aortic wall might generate, rather than absorb, mechanical energy during stretch (273); however, in view of the fact that the transducer was an elastic tube containing a dense liquid (mercury), it seems best to await the publication of dynamic calibration data in order to be certain that the reported effect was not due to the properties of the instrument. In another study, the motion of beads, sewn on the surface of the aorta, has been recorded by means of cinephotography and correlated with intravascular pressure changes. Although the relationships are complex, "conventional hysteresis loops" were obtained (274).

An interesting theoretical consideration of the transmission of transient disturbances in a viscoelastic medium has been attempted with the use of capacitance-resistance electrical circuits. The mathematical representation, however, converged too slowly to be of practical use (275). While it has become commonplace to use electrical circuits to represent more complex fluid systems, it should be remembered that to be useful such a circuit must be analogous to the system it is supposed to represent. Until the properties of the vascular system are evaluated, the use of such analogues may be misleading.

The vasculature is a complex geometric array of vessels each having different physical properties and together they form a "system" whose properties and behavior are quite different from the individual vessels of which it is composed. One popular view in that the system has the properties and behavior of a single compression chamber (Windkessel with a resistance (arterioles) at its "end." It is commonly implied that the arteries forming the Windkessel exhibit negligible resistance to flow but function primarily as a distensible storage chamber and that the significant peripheral resistance is truly peripheral. A somewhat simplified review of some of the considerations and methods used in "system" analysis as contrasted to the analysis of separate parts of the vascular system has been published (276). It was concluded that it was unlikely that the arterial system behaves like such a simple Windkessel system.

An extension of the Windkessel concept holds that the arterial system is a resonating chamber in that pressure waves reflected from the periphery (arterioles) become fused with the wave transmitted from the root of the aorta, thus producing the distortions that the arterial pulse undergoes during its transmission. Recently, detailed studies of the distortions of the arterial pressure pulse that occur in humans during the Valsalva maneuver (277), and exercise and tilt (278) have been reported, and it was suggested that reflected waves were responsible for the observed distortions. More recently, however, there have been studies and considerations of the arterial system leading to the conclusions that it is unlikely that there are any natural, discrete reflections occurring in the arterial system, and that the distortion results from the fact that the pressure pulse generated in the root of the aorta is a complex wave which can be considered to be made up of a number of harmonics. Due

to the "mass" and "viscous" properties of the blood and vessels, each of these harmonics will travel at different velocities and be subject to selective damping; therefore, the pulse will become distorted as it traverses the arterial system (279, 280). Theoretically, the continuous variations in vascular geometry due to branching and diameter change of the vessels and the stiffness[9] and damping properties of the vessel walls make the reflected, and particularly the standing wave, hypothesis improbable. The question of pressure wave reflection from an occluding arterial pressure cuff has been considered, and the conclusions were that, although distortions due to the cuff are possible, it is doubtful whether any discrete effects occur since many other assymetrical phenomena are also present (281). Studies of pulsatile pressure and flow data, in the dog's femoral artery, have been interpreted as evidence for vascular resonance effects (282). It would seem that the existence of true significant "resonance" within the arterial system is unlikely, since the existence of discrete pressure reflection is unlikely. It is possible that these apparent resonance effects are, in reality, manifestations of selective damping.

Much of the motivation for considering the properties and behavior of the arterial system appears to arise from the desire to calculate stroke volume from pulse pressure, as the latter is relatively easier to obtain than the former. The old adage about lifting oneself by one's own bootstrap might be applied to many such attempts. Most equations that have been published range from simple ones containing the pulse pressure and certain variables having no direct relationship to cardiac output (e.g., age, weight, sex, etc.) to more complex equations which are fundamentally derived from the Windkessel model and use the velocity of some part of a complex, changing pressure pulse as a measure of arterial distensibility. Recently the equation of a wave in an even simpler (viscosity neglected) distensible tube system was again derived and proposed as a formula for calculating stroke volume (283). A considerably more elaborate analysis of complex electrical circuits (transmission lines) has been compiled, and it was concluded that when certain parameters of the circuit were lumped and "non-end" resistances were neglected, the final equations looked very much like the Windkessel equations proposed by physiologists many years ago (284, 285, 286).

The usefulness of analyses made on single pressure pulses has been criticised on the grounds that a single pulse is not a discrete event (287). This criticism has been answered by recalling that most, if not all, methods that have been devised to study hemodynamic properties associated with

[9] The classical term "tone" has limited physical meaning since the physical properties of a tube are determined by the modulus of elasticity, wall thickness, and tube radius. If dynamic stress is applied to the wall, the tube response is also dependent upon wall "viscosity" and "mass." A more appropriate term might be that used in the physical sciences to describe the net effect of these parameters, i.e., stiffness.

wave motion (including Fourier analysis) imply superposition of events; thus, if any of these methods is reliable, so is single pressure pulse analysis (288).

A number of general relationships of pressure changes within the vascular system has been reported. It has been stated that a pressure reference point which is "extremely precise" and invariant even from dog to dog has been located. It was postulated that this point is the locus of a feedback relationship between end-diastolic pressure and cardiac output (289). Two curves of pressure changes (one with a known volume change superposed upon the unknown) have been measured in the aorta after cessation of inflow from the heart, and having neglected any considerations of flow within the vascular system, it was concluded that the venous side was 18 to 30 times more distensible than the arterial side (290). In another study pressure changes with respect to time were measured in the central veins and aorta after flow in or out of the system was blocked. Although the data included only pressure measurements, they indicated that as the arterial pressure falls, the venous pressure rises, therefore making possible the existence of a positive arterial pressure with zero pressure gradient between arteries and veins (291). Again, it has been found, by using a pump with known output in lieu of the heart, that the relationship of pulse pressure to stroke volume in the arterial system is nonlinear (292, 293). This relationship is also observable using indirect criteria for determining the stroke volume of the heart (294).

Additional measurements have been made of the time relationships of pressures in the various chambers of the heart and great vessels and electrocardiographs in man (295, 296). Comparisons of oscillograms of the peripheral arteries obtained from the skin surface in normal and diseased conditions (297) and with the electrocardiograph (298) have appeared. An interesting approach to the study of the shearing forces in tissues surrounding a ruptured aneurism has appeared (299). It continues to be evident that estimations of the size of vascular orifices (e.g., patent ductus arteriosus) from pressure measurements do not take into account the effects of pulsatile flow (300).

There is little doubt that the walls of veins are capable of exerting marked changes in the distensibility and flow resistance in the "low pressure-highly distensible" side of the vascular circuit. Many experiments on various preparations under different conditions attest to the general conclusion that venomotor activity is variably affected by epinephrine, norepinephrine, acetylcholine, autonomic reflexes, and disease (301 to 307). Specific volume regulation is also implied in venomotor activity (301, 307).

A book has been published that should be very useful to graduate students in physiology. It contains two sections related to the circulation. Elementary concepts of the essential parameters of hemodynamics are developed clearly and well, and some views of the properties and behavior of the vascular system are uncritically presented (308).

Throughout the literature there appear experimental evidence and considerations that Poiseuille's equation does not express the conditions existing in the vascular system (cf. Ref. 309). It is doubtful that the parameter of a coefficient of viscosity should be applied to blood. The definition of a viscosity coefficient is obtained by assuming that there is a linear relation between shear stress and shear rate of strain in the liquid. Blood is not such a liquid, and so the "effective" viscosity of blood depends upon the system through which it flows, and in any system the "coefficient" would not be constant with respect to velocity. In an interesting consideration of the anatomy of vessels is contained the reminder that "apparent" viscosities have no comparative value; also described are a number of geometrical aspects of blood vessels that further affect the Poiseuille parameters, e.g., arterial vessels are conical rather than cylindrical (310). Attempts have been made to correlate viscosimeter measurements of blood and *in vivo* visual changes in apparent viscosity due to red corpuscle aggregation (311). Modified viscosimeters for blood have been described (312, 313).

The commonest use to which the Poiseuille relationship is applied is the calculation of "peripheral resistance" and thus, indirectly, to the calculation of changes in vascular "tone.[9] Two clever devices have been proposed for the measurement of wall tone in small vessels in which there is steady flow (314, 315).

Another popular concept is that calculated total peripheral resistance resides primarily in the most peripheral arteries and arterioles. Such a concept may be questioned, since this form of resistance is resistance per unit length of vessel. While it is true that the resistance per unit length in the collective arteriolar bed is somewhat greater than that in vessels just proximal to the arterioles, and so on back through the vast branching of the arterial system into the root of the aorta, it is also true that the length of the arteriole is very small and, furthermore, the vessels are mostly in parallel. This resistance may be considered as increasing like the volume of a flaring horn, and cutting off a short portion of the end of the horn will alter its volume very little. It is possible, therefore, that the resistance of the arterioles constitutes but a small proportion of the arterial system's total resistance.

Physiological Stresses

Hypovolemic or hemorrhagic and tourniquet "shock."—In addition to previously considered studies dealing with hemorrhage, the following are of interest: in dogs bled to death stepwise it was found, by bioassay, that large amounts of epinephrine, appeared in the circulating blood (316). Measurements of adrenal venous blood content of corticosteroids during hemorrhage suggests that their secretion does not correlate with the tolerance to shock (317). The "hypovolemic shock" produced by intraperitoneal injections of fecal suspensions could be corrected only by combining antibiotic with fluid therapy (318). It has, again, been suggested that *in vivo* coagulation of blood

is a factor in causing irreversible shock (319). Studies of humans, subjected to moderate hemorrhage, have indicated that "central" venous pressure decreased by an average of 0.7 cm. H_2O per 100 cc. blood withdrawn; however, the term $\Delta P/\Delta V$, used to express this relationship, may be misleading (320). Reticulocyte and hemoglobin studies suggest complete recovery in 3 to 4 weeks from the effects of small (8 per cent of estimated blood volume) blood losses in normal humans (321).

Studies have indicated that the increase in cardiac output which accompanies hypervolemic anemia is related to the anemia and not to the increase in blood volume (322). Studies of tourniquet shock in mice have indicated that saline and serum therapy produced similar survival rates when given immediately, while after five hours serum was considerably more effective (323), and massive infusions of saline may reverse terminal shock (324).

Gravity.—A comparison of intra-arterial pressure curve responses following tilting from the recumbent to the head-up position has been made between normal and orthostatic hypotensive humans, and it has been suggested that a mixture of ephedrine and theophylline (Peripherin-Homburg) may be beneficial to the latter (325). A general discussion of therapy for orthostatic hypotension has also appeared (326). A report on various types of G-suits and their efficacy in preventing hypotensive effects at higher than one G has been published (327). A study of pulmonary congestion that may occur with the use of G-suits at high G has been made and correlated with modifying effects of norepinephrine (328).

High altitude, low oxygen, asphyxia and high carbon dioxide.—The effects of placing animals in a "biological vacuum" (30 mm. Hg) have been studied, and it was concluded that respiratory and circulatory collapse was attributable, in sequence, to: expansion of visceral gases, release of dissolved gases and vaporization (boiling) of body fluids (329). It is claimed that "aeroembolism" at current flight altitudes is caused by extra- rather than intravascular bubbles (330). Pathological findings in fatal rapid decompression of man have been described (331). Data indicate that both the systemic and central blood volume are increased in persons living at high altitude (332). Puppies born at a stimulated 20,000 feet altitude showed a marked increase in the capillary-tissue area ratio (333). Frequent asphyxia in rats results in a prolonged but reversible hypertension unaccompanied by adrenal hyperplasia (334). In dogs, respiratory arrest caused by curare (D-tubocurarine) resulted in a pulmonary and systemic hypertension whether or not hypoxia was present (335). Hypotension in dogs, produced by switching the inspired mixture from 30 per cent CO_2 to 100 per cent O_2, was again found to result from a fall in cardiac output (336).

Exercise.—Confirmatory evidence has been obtained for the belief that the athlete and the nontrained individual, when exercising, increase cardiac output and oxygen extraction at the same rate (139). Studies of unanesthe-

tized exercising dogs indicate that there is also a linear relationship between work and cardiac output. It was suggested that there is a constant muscle A-V O_2 difference of about 14 volumes per cent and that there may be flow through muscle arteriovenous shunts at rest but not during exercise (140). Evidence indicates that the brain does not share in the overall lowering of "total peripheral resistance" during exercise (337). In a review of the regulation of cardiac output during exercise, the question of regional vasoconstriction to offest the lower resistance through muscle and skin has been considered (338). It is reported that anemic and thyrotoxic humans who have a high resting cardiac output also have a higher than normal increase therein during exercise (339). Measurements made again indicate that the central venous blood oxygen content decreases while the cardiac output increases during pregnancy (340).

Noise and sounds.—It is not surprising to learn that the differences in the arterial pressure response to sounds are dependent upon emotional reactions (341). It is surprising, however, to learn that cardiovascular changes can occur in individuals listening to pure tones that are not related to emotional responses (342).

Electric shock.—It is reported that this form of stress causes generalized, as well as cerebral, vasodilation (343). It is also suggested that increased vagal activity accounts for the usual vascular responses and that they can be somewhat reversed by gallamine triethiodide (Flaxedil, a curare-like drug) (344). It has been reported that convulsive shocks induce the liberation of some substance that increases the epinephrine sensitivity in the rat mesoappendix (345).

General Interest

The association of hypertension and aversion to sodium chloride is of interest. It has been reported that in rats, made hypertensive by wrapping the kidneys, the hypertension precedes the aversion and the degree of aversion apparently depends upon a number of factors, including the severity of the hypertension. No correlation with the blood level of sodium was found (346, 347). It has been reported that systemic venous and pulmonary venous blood flow in the common ventricle of the tortoise may remain separate (348). When dogs smoke cigarettes, their blood electrolytes alter in variable fashions and the eosinophils almost disappear, suggesting a release of epinephrine (349). A review of cardiovascular changes associated with collagen diseases has been published (350). The complexities of developing conditioned cardiovascular reflexes has been dealt with (351). The effects of age and sex on certain cardiovascular parameters in the human (352, 353) and the duck and pigeon (354) have been measured. It has been reported that heparin is more effective in preventing serum induced thrombosis than is dicmarol (355). Adenosinetriphosphate appeared to inhibit cholesterol and epinephrine-thyroxine induced atherosclerosis, whereas adenosine monophosphate and

heparin did not (356). The differences in arterial pressure responses between normal persons and those with congestive failure performing the Valsalva maneuver have been explained mainly on the basis of the increased venous pressure in the latter condition (357). Evidence has accrued that, following obstruction of the thoracic aorta, collaterals develop between the upper thoracic and abdominal aorta (358).

Methods

Blood flow.—An excellent review of the historical development of dilution techniques for measuring blood flow, and in particular cardiac output, has appeared (359). Certain aspects of newer techniques, however, could have been covered somewhat more adequately. Recently, for example, renewed attempts have been made to utilize constant infusions of indicator into the aorta; a method which, theoretically, has fewer uncertainties and variables and thus provides a more direct measure of flow than the single "slug" of indicator injected to the right of the lungs. The constant infusion technique was questioned on the grounds that it was "doubtful" whether an equilibrium plateau can be reached or that adequate mixing can occur. The published evidence, it seems to this author, for the development of a plateau and for mixing is sound, particularly when the indicator is infused into the root of the aorta where the flow is normally unstable; but whether this applies for peripheral intra-arterial injections is doubtful. The use of the continuous injection technique has been extended to include injections into the right ventricle, pulmonary artery (360), and thoracic aorta (361) of man. Two recent theoretical considerations of the single slug dilution curves have appeared; one is a general consideration of detection methods and sampling sites with respect to mixing sites (362), the other an attempt to extrapolate from a systemic arterial sampling site to the pulmonary vein in order to calculate pulmonary and left heart blood volume more accurately (363, 364). A reiteration of some of the conditions in which the Fick method is more applicable than the dilution method, and vice versa has been published (365). One of the limitations of dye dilution techniques is the recirculation and intravascular retention of indicator. The utility of indigo carmine has been tested and this dye was found to leave the vascular system more rapidly (half-time approximately 4½ min.) than T-1824 (366). Another problem is that variations of the oxygen saturation affect measurement of the concentration of T-1824 in whole blood, and two devices have been described that reportedly reduce or eliminate this difficulty (367, 368). The applicability of I^{131} HSA and tagged (P^{32}) red corpuscles in estimating flow and volume by the dilution technique have been elaborated (369, 370). Applications of the ear oximeter have been extended (371). A method for estimating the content of T-1824 in homogenized tissue has been described, and the data obtained confirm previous results (372).

The Fick principle using PAH has been applied to the estimation of in-

ferior vena caval blood flow (373). Uncertainties in evaluating the occurrence of concentration equilibrium with the N_2O technique have been re-emphasized (374).

Studies and modifications of the diathermic flow meter of Rein have appeared (44, 375, 376). Certain advantages and disadvantages of an automatically recording bubble flow meter have been investigated (377). A modification of the acetylene method for estimating cardiac output by using an infrared absorption device has been tested (378). A differential pressure (Venturi) flow meter for use with arterial loops has been described (379). A number of publications concerning the ballistocardiogram have appeared; they relate to standardization, correlation with injections of blood into cadavers and studies in patients with mitral and coronary heart disease (380 to 387). Comparisons have been made between the cardiac output obtained by the Fick method and calculated from the pulse pressure by the method of Starr and of Wezler and Boger. The correlations were found to be poor indeed (388). A discussion of resistance flow meters has appeared (389).

Blood pressure.—An extensive bibliography relative to blood pressure measuring devices has been published (390). A method reportedly for the measurement of blood pressure leaves open to the reader the matter of calibration (391). A method for implanting catheters into rats' aortae for long periods has been described (392). In dwelling intra-arterial cannulae for measuring pressures in the horse have been described (393). Another device for providing instantaneous or average records or both from an electrical manometer has been described (394). It is this author's impression that many modifications of capacitance, inductance, and resistance-pressure transducers are being developed by many industrial firms, and their value will be assessed in time.

Lateral positioning of the human body and measuring the pressure in the distended, dependent arm vein has been described as a method for measuring "central" venous pressure (395). An automatic method for measuring arterial pressure pulse wave velocity, which utilizes the distance between pulse peaks, has been described (396). Many previous workers have shown, however, that the time interval between systolic pressure peaks is of limited usefulness, and the estimated wave velocity obtained therefrom is quite different from that obtained from "foot to foot" measurements.

A most interesting and straightforward technique for recording directly the pressures in the pulmonary artery, aorta, and left atrium of man by inserting a needle percutaneously through the suprasternal notch has been applied in a variety of clinical conditions (397–400).

Other techniques of interest.—An effective cinefluorographic technique for visualizing flow patterns in the heart and large vessels has been described (401). This author has observed films obtained by this technique and was impressed by how nicely the unstable flow in the aorta could be seen. Another consideration of exposure times for cinefluorography of cardiovascular events

and devices for attaining these requirements has appeared (402). A technique for microradioangiography has been described (403).

Additional studies of a modified platinum electrode for measuring the oxygen tension on whole blood have been reported (404). An improved technique for establishing cross circulation is described and evaluated (405). A multiway stopcock for rapid changes to various flow velocities has been described (406). In view of the difficulties in obtaining complex or expensive recording equipment in some areas, a discussion of the value of substitutes has been published (407). In a well-written and comprehensive monograph, many aspects of venous physiology and their relationships to cardiopulmonary function have been integrated (409).

An excellent and extensive account of techniques for the diagnosis and evaluation of patients with cardiovascular abnormalities has been published (408).

Conclusion.—There is some degree of mixed emotion accompanying the knowledge that cardiovascular physiology is still very much in the descriptive phase and is therefore still a land of promise for investigators.

LITERATURE CITED

1. Barcroft, H., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, 9 (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
2. Barcroft, H., and Cobbold, A. F., *J. Physiol. (London)*, **132,** 372 (1956)
3. Barcroft, H., and Cobbold, A. F., *J. Physiol. (London)*, **131,** 10P (1956)
4. Barcroft, H., Bock, K. D., and Hensel, H., *Pflügers Arch. ges. Physiol.*, **261,** 199 (1955)
5. Barcroft, H., and Cobbold, A. F., *J. Physiol. (London)*, **132,** 10P (1956)
6. Barcroft, H., Edholm, O. G., Foster, C. A., Fox, R. H., and Macpherson, R. K., *J. Physiol. (London)*, **132,** 16P (1956)
7. Roddie, I. C., Shepherd, J. T., and Whelan, R. F., *J. Physiol. (London)*, **132,** 47P (1956)
8. Edholm, O. G., Fox, R. H., and Macpherson, R. K., *J. Physiol. (London)*, **132,** 15P (1956)
9. Gaskell, P., *J. Physiol. (London)*, **131,** 647 (1956)
10. Gaskell, P., *J. Physiol. (London)*, **131,** 639 (1956)
11. Roddie, I. G., and Shepherd, J. T., *J. Physiol. (London)*, **131,** 657 (1956)
12. Cooper, K. E., Ferres, H. M., and Mottram, R. F., *J. Physiol. (London)*, **131,** 29P (1956)
13. Duff, R. S., *J. Physiol. (London)*, **129,** 53 (1955)
14. Folkow, B., *Physiol. Revs.*, **35,** 629 (1955)
15. Szücs, E., Heténvi, E., and Went, I., *Acta Physiol. Acad. Sci. Hung.*, **9,** 24 (1956) Suppl.
16. Went, I., Szücs, E., and Heténvi, E., *Acta Physiol. Acad. Sci. Hung.*, **9,** 193 (1955)
17. Patterson, G. C., and Whelan, R. F., *Clin. Sci.*, **14,** 197 (1955)
18. Duff, F., Patterson, G. C., and Whelan, R. F., *Clin. Sci.*, **14,** 267 (1955)
19. Tripod, J., and Wirz, E., *Arch. intern. Pharmacodynamie*, **102,** 187 (1955)
20. Patterson, G. C., *Clin. Sci.*, **15,** 17 (1956)
21. Beaconsfield, P., and Ginsburg, J., *Circulation Research*, **3,** 478 (1955)
22. Coles, D. R., and Greenfield, A. D. M., *J. Physiol. (London)*, **131,** 277 (1956)
23. Pappenheimer, J. R., and Soto-Rivera, A., *Am. J. Physiol.*, **152,** 471 (1948)
24. Greenfield, A. D. M., and Patterson, G. C., *J. Physiol. (London)*, **131,** 290 (1956)
25. Wood, J. E., and Eckstein, J. W., *J. Clin. Invest.*, **35,** 746 (1946)
26. Allwood, M. J., *Circulation Research*, **4,** 268 (1956)
27. Gaskell, P., *J. Physiol. (London)*, **131,** 627 (1956)
28. Burch, G. E., *Circulation*, **13,** 641 (1956)
29. Roddie, R. A., *J. Appl. Physiol.*, **8,** 67 (1955)
30. Coles, D. R., *J. Physiol. (London)*, **131,** 5P (1956)
31. Shanks, R. G., *Clin. Sci.*, **14,** 285 (1955)
32. Coles, D. R., Kidd, B. S. L., and Patterson, G. C., *J. Physiol. (London)*, **132,** 46P (1956)
33. Schröder, J., and Voridis, E., *Pflügers Arch. ges. Physiol.*, **261,** 550 (1955)
34. Montgomery, H. F., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, **92** (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
35. Aschoff, J., *Pflügers Arch. ges. Physiol.*, **261,** 264 (1955)
36. Mottram, R. F., *J. Physiol. (London)*, **130,** 42P (1955)
37. Love, A. H., *Clin. Sci.*, **14,** 275 (1955)

38. Rosensweig, J., *J. Physiol. (London)*, **129**, 281 (1955)
39. Hensel, H., Ruef, J., and Colenhofen, K., *Angiology*, **6**, 190 (1955)
40. Burton, A. C., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, **43** (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
41. Bock, K. D., Hensel, H., and Ruef, J., *Pflügers Arch. ges. Physiol.*, **261**, 322 (1955)
42. Franke, H., and Schroeder, J., *Klin. Wochschr.*, **33**, 833 (1955)
43. Gottstein, U., and Hille, H., *Z. Kreislaufforsch.*, **44**, 433 (1955)
44. Wever, R., *Pflügers Arch. ges. Physiol.*, **262**, 1 (1955)
45. Walder, D. N., *Clin. Sci.*, **14**, 303 (1955)
46. *Vascular Patterns as Related to Function, 2nd Conf. Microcirculatory Physiology and Pathology* (Williams and Wilkins Co., Baltimore, Md., 132 pp., 1955) (Reprinted from *Angiology* **6**, 281–413, 1955)
47. Piiper, J., and Schuermeyer, E., *Pflügers Arch. ges. Physiol.*, **261**, 234 (1955)
48. Prerovsky, I., and Linhart, J., *Časopis lékařů Českých*, **94**, 260 (1955)
49. Prerovsky, I., Linhart, J., and Fejfar, Z., *Ceskosl. Fysiol.*, **4**, 389 (1955)
50. Gerova, M., and Madlafousek, J., *Ceskosl. Fysiol.*, **5**, 100 (1956)
51. Dörner, J., *Pflügers Arch. ges. Physiol.*, **262**, 265 (1956)
52. Cobbold, A. F., and Lewis, O. J., *J. Physiol. (London)*, **132**, 379 (1956)
53. Lindgren, P. and Uvnäs, B., *Acta Physiol. Scand.*, **33**, 108 (1955)
54. Howell, F. R., and Richards, T. G., *J. Physiol. (London)*, **130**, 414 (1955)
55. Phillips, F. A., Jr., Brind, S. H., and Levy, M. N., *Circulation Research*, **3**, 357 (1955)
56. Levy, M. N., *Federation Proc.*, **15**, 118 (1956)
57. Haddy, F. J., and Gilbert, R. P., *Circulation Research*, **4**, 25 (1956)
58. Tripod, J., and Wirz, E., *Arch. intern. Pharmacodynamie*, **102**, 335 (1955)
59. Tripod, J., and Wirz, E., *Arch. intern. Pharmacodynamie*, **105**, 73 (1956)
60. Tobian, L., and Fox, A., *J. Clin. Invest.*, **35**, 297 (1956)
61. Macher, E., *Klin. Wochschr.*, **34**, 391 (1956)
62. Di Salvo, R. J., Bloom, W. L., Brust, A. A., Ferguson, R. W., and Ferris, E. B., *J. Clin. Invest.*, **35**, 568 (1956)
63. French, E. B., and Kilpatrick, R., *Clin. Sci.*, **14**, 639 (1955)
64. Godden, J. O., Roth, G. M., and Hines, E. A., *Circulation*, **12**, 963 (1955)
65. Mackay, I. F. S., *J. Appl. Physiol.*, **8**, 169 (1955)
66. Mackay, I. F. S., *J. Appl. Physiol.*, **8**, 173 (1955)
67. Mackay, I. F. S., *J. Appl. Physiol.*, **8**, 241 (1955)
68. Metz, D., *Klin. Wochschr.*, **33**, 838 (1955)
69. Kramer, K., Graf, K., and Overbeck, W., *Pflügers Arch. ges. Physiol.*, **262**, 285 (1956)
70. Pappenheimer, J. R., and Kinter, W. B., *Am. J. Physiol.*, **185**, 377 (1956)
71. Kinter, W. B., and Pappenheimer, J. R., *Am. J. Physiol.*, **185**, 391 (1956)
72. Kinter, W. B., and Pappenheimer, J. R., *Am. J. Physiol.*, **185**, 399 (1956)
73. Lilienfield, L. S., Porfido, F. A., and Rose, J. C., *J. Clin. Invest.*, **35**, 721 (1956)
74. Piiper, J., and Schuermeyer, E., *Pflügers Arch. ges. Physiol.*, **261**, 543 (1955)
75. Ochwadt, B., *Pflügers Arch. ges. Physiol.*, **262**, 207 (1956)
76. Brull, L., Louis-Bar, D., and Lybeck, H., *Acta Physiol. Scand.*, **34**, 175 (1955)
77. Cerletti, A., Carpi, A., and Rothlin, E., *Helv. Physiol. et Pharmacol. Acta*, **13**, C8 (1955)
78. Little, J. M., Kelsey, W. M., and Yount, E. H., Jr., *Am. J. Physiol.*, **185**, 159 (1956)

79. Judson, W. E., Hollander, W., Hatcher, J. D., and Halperin, M. H., *J. Clin. Invest.*, **34,** 1546 (1955)
80. Brun, C., Crone, C., Davidsen, H. G., Fabricius, J., Hansen, A. T., Lassen, N. A., and Munck, O., *Proc. Soc. Exptl. Biol. Med.*, **89,** 687 (1955)
81. Werkö, L., Bergström, J., Bucht, H., Ek, J., Eliasch, H., Eriksson, K., Thomasson, B., and Varnauskas, E., *Circulation*, **13,** 187 (1956)
82. Moeller, J., *Z. Kreislaufforsch.*, **44,** 501 (1955)
83. Lequime, J., and Verbanck, M., *Cardiologia*, **26,** 257 (1955)
84. Poutasse, E. F., *Circulation*, **13,** 37 (1956)
85. Schwalb, H., and Schimmler, W., *Klin. Wochschr.*, **33,** 921 (1955)
86. Rotter, W., *Münchener Med. Wochschr.*, **97,** 1198 (1955)
87. Gregg, D. E., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, **232** (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
88. Gregg, D. E., *Verhandl. deut. Ges. Kreislaufforsch.*, **21,** 22 (1956)
89. Heidenreich, O., and Schmidt, L., *Klin. Wochschr.*, **34,** 477 (1955)
90. Laurent, D., Bolene-Williams, C., Williams, F. L., and Katz, L. N. *Am. J. Physiol.*, **185,** 355 (1956)
91. Aykut, R., *Arch. intern. pharmacodynamie*, **102,** 217 (1955)
92. Wolf, M. M., and Berne, R. M., *Circulation Research*, **4,** 343 (1956)
93. Campeti, F., Gramiak, R., Watson, J. S., Ramsey, G. H., and Weinberg, S., *Circulation*, **12,** 199 (1955)
94. Hort, W., *Virchow's pathol. Anat. Physiol.*, **327,** 561 (1955)
95. Sinizyn, N. P., *Klin. Wochschr.*, **34,** 218 (1956)
96. Hackel, D. V., Sancetta, S. M., and Kleinerman, J., *Circulation*, **13,** 92 (1956)
97. Rowe, G. G., Huston, J. H., Weinstein, A. B., Tuchman, H., Brown, J. F., and Crumpton, C. W., *J. Clin. Invest.*, **35,** 272 (1956)
98. Russek, H. I., Zohman, B. L., Drumm, A. E., Weingarten, W., and Dorset, V., *Circulation*, **12,** 196 (1955)
99. Bakst, A. A., Maniglia, R., and Bailey, C. B., *J. Clin. Invest.*, **35,** 302 (1956)
100. Patterson, J. L., Jr., Heyman, A., Battey, L. L., and Ferguson, R. W., *J. Clin. Invest.*, **34,** 1857 (1955)
101. Sokoloff, L., Wechsler, R., Kennedy, R. L., and Kety, S. S., *J. Clin. Invest.*, **34,** 1101 (1955)
102. Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., and Kety, S. S., *J. Clin. Invest.*, **34,** 1092 (1955)
103. Koch, D., and Schnellbacher, F., *Klin. Wochschr.*, **33,** 668 (1955)
104. Morello, A., Bartecek, A., Stellar, S., and Cooper, I. S., *Angiology*, **7,** 16 (1956)
105. Lewis, B. M., Sokoloff, L., Wechsler, R. L., Wentz, W. B., and Kety, S. S., *U. S. Bur. Med. Surg.* (Project NM001 100 301 #8, 1956)
106. Schimmler, W., *Z. Kreislaufforsch.*, **45,** 47 (1956)
107. Moskalienko, Y. E., and Naumienko, A. I., *Fiziol. Zhur., S.S.S.R.*, **42,** 312 (1956)
108. Meyers, J. D., *Shock and Circulation Homeostasis, Trans. 4th Conf.*, **121** (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
109. Andrews, W. H. H., Maegraith, B. G., and Richards, T. G., *J. Physiol. (London)*, **131,** 669 (1956)
110. Taylor, W. J., and Meyers, J. D , *Circulation*, **13,** 368 (1956)
111. Bennati, D., Ghiggino, C. W., and Zerbino, V., *Compt. rend. soc. biol.*, **149,** 1705 (1955)
112. Egeli, E. S., and Reimann, F., *Klin. Wochschr.*, **33,** 1055 (1955)

113. Graf, W., Porjé, I. G., and Allgoth, A. M., *Gastroenterologia*, **83**, 233 (1955)
114. Egeli, E. S., and Reimann, E., *Klin. Wochschr.*, **33**, 435 (1955)
115. de Sousa, A., and Cruz, J. M., *Compt. rend. soc. biol.*, **149**, 436 (1955)
116. Baez, S., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, **112** (Josiah Macy, Jr. Foundation, New York, N. Y., 291 pp., 1955)
117. Popper, H. L., Jefferson, N. C., Hassan, M. I., Phillips, C. W., Proffitt, M. M., and Necheles, H., *Am. J. Physiol.*, **183**, 235 (1955)
118. Jefferson, N. C., Hassan, M. I., Popper, H. L., and Necheles, H., *Am. J. Physiol.*, **184**, 589 (1956)
119. Popper, H. L., Jefferson, N. C., and Necheles, H., *Am. J. Physiol.*, **185**, 125 (1956)
120. Schorn, J., *Münchener med. Wochschr.*, **97**, 1199 (1955)
121. Riecker, G., *Pflügers Arch. ges. Physiol.*, **262**, 37 (1955)
122. Wheeler, H. O., Combes, B., Childs, A. W., and Wade, O. L., *Transactions Association American Physicians*, **68**, 177 (1955)
123. Selkurt, E. E., *Proc. Soc. Exptl. Biol. Med.*, **90**, 427 (1955)
124. Brickner, E. W., Dowds, E. G., Willitts, B., and Selkurt, E. E., *Am. J. Physiol.*, **184**, 275 (1956)
125. Deal, C. P., Jr., and Green, H. D., *Circulation Research*, **4**, 38 (1956)
126. Andrews, W. H. H., Hecker, R., Maegraith, B. G., and Ritchie, H. D., *J. Physiology (London)*, **128**, 413 (1955)
127. Szilágyi, T., Kocsár, L., and Kesztyüs, L., *Acta Physiol. Acad. Sci. Hung.*, **8**, 405 (1955)
128. Dontas, A. S., *Circulation Research*, **3**, 363 (1955)
129. Reynell, P. C., Marks, P. A., Chidsey, C., and Bradley, S. E., *Clin. Sci.*, **14**, 407 (1955)
130. Sapirstein, L. A., Buckley, N. M., and Ogden, E., *Science*, **122**, 1138 (1955)
131. Cull, T. E., Scibetta, M. P., and Selkurt, E. E., *Am. J. Physiol.*, **185**, 365 (1956)
132. Marks, P. A., Reynell, P. C., and Bradley, S. E., *Am. J. Physiol.*, **183**, 144 (1955)
133. Klopper, P. J., *J. Physiol. (London)*, **129**, 547 (1955)
134. Rose, J. C., Cosimano, S. J., Jr., Hufnagel, C. A., and Massullo, E. A., *J. Clin. Invest.*, **34**, 1625 (1955)
135. Henry, J. P., Gauer, O. H., and Sieker, H. O., *Circulation Research*, **4**, 91 (1956)
136. deBurghDaly, I., *J. Physiol. (London)*, **132**, 42P (1956)
137. Rose, J. C., Freis, E. B., Hufnagel, C. A., and Massullo, E. A., *Am. J. Physiol.*, **182**, 197 (1955)
138. Shadle, O. W., Moore, J. T., and Billig, D. M., *Circulation Research*, **3**, 385 (1955)
139. Freedman, M. E., Snider, G. L., Brostoff, P., Kimelblot, S., and Katz, L. N., *J. Appl. Physiol.*, **8**, 37 (1955)
140. Barger, A. C., Richards, V., Metcalfe, J., and Günther, B., *Am. J. Physiol.*, **184**, 613 (1956)
141. Courtoy, P., and Salonikides, N., *Acta Cardiol.*, **11**, 52 (1956)
142. Price, K. C., Hata, D., and Smith, J. R., *Am. J. Physiol.*, **182**, 183 (1955)
143. Niden, A. H., and Aviado, D. M., Jr., *Circulation Research*, **4**, 67 (1956)
144. Bostroem, B., and Piiper, J., *Pflügers Arch. ges. Physiol.*, **261**, 165 (1955)
145. Bartels, H., Beer, R., Fleischer, E., Hoffheinz, H. J., Krall, J., Rodewald, G., Wenner, J., and Witt, I., *Pflügers Arch. ges. Physiol.*, **261**, 99 (1955)
146. Leusen, I., and Demeester, G., *Acta Cardiol.*, **10**, 556 (1955)

147. Cournand, A., *Acta Cardiol.*, **10,** 429 (1955)
148. Hertz, C. W., *Klin. Wochschr.*, **34,** 472 (1956)
149. Cournand, A., *Shock and Circulatory Homeostasis, Trans. 4th Conf.*, **166** (Josiah Macy, Jr., Foundation, New York, N. Y., 291 pp., 1955)
150. Venrath, H., Lechtenbörger, H., Valentin, H., and Bolt, W., *Z. Kreislaufforsch.*, **44,** 544 (1955)
151. Carlill, S. D., and Duke, H. N., *J. Physiol.* (*London*), **131,** 12P (1956)
152. Vuylsteek, K., and Leusen, I., *Arch. intern. physiol.*, **63,** 422 (1955)
153. deBurghDaly, M., and Schweitzer, A., *J. Physiol.* (*London*), **131,** 220 (1956)
154. Lee, G. D. J., and DuBois, A. B., *J. Clin. Invest.*, **34,** 1380 (1955)
155. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L., *Am. J. Physiol.*, **185,** 127 (1956)
156. Cherniack, R. M., Farhi, L. E., Armstrong, B. W., and Proctor, D. W., *J. Appl. Physiol.*, **8,** 203 (1955)
157. Mead, J., and Gaensler, E. A., *Federation Proc.*, **15,** 127 (1956)
158. van Buchem, F. S. P., *Circulation*, **13,** 719 (1956)
159. Williams, M. H., Jr., and Towbin, E. J., *Circulation Research*, **3,** 422 (1955)
160. Wasserman, K., and Mayerson, H. S., *Am. J. Physiol.*, **182,** 419 (1955)
161. Wasserman, K., Joseph, J. D., and Mayerson, H. S., *Am. J. Physiol.*, **184,** 175 (1956)
162. Wasserman, K., Loeb, L., and Mayerson, H. S., *Circulation Research*, **3,** 594 (1955)
163. Pirani, C. L., Juster, R., Froeb, H. F., Consolazio, C. F., and Ingraham, R. G., *J. Appl. Physiol.*, **8,** 193 (1955)
164. Benson, J. A., Jr., Kim, K. S., and Bollman, J. L., *Am. J. Physiol.*, **182,** 217 (1955)
165. Mandel, M. J., Vidt, D. G., and Sapirstein, L. A., *Am. J. Physiol.*, **182,** 428 (1955)
166. Sapirstein, L. A., Buckley, N. M., and Ogden, E., *Am. J. Physiol.*, **183,** 178 (1955)
167. Renkin, E. M., *Am. J. Physiol.*, **183,** 125 (1955)
168. Enns, T., and Chinard, F. P., *Am. J. Physiol.*, **185,** 133 (1956)
169. Grim, E., Lee, J. S., and Visscher, M. B., *Am. J. Physiol.*, **182,** 359 (1955)
170. Rondell, P. A., Keitzer, W. F., and Bohr, D. F., *Am. J. Physiol.*, **183,** 523 (1955)
171. Bloch, E. H., *Angiology*, **6,** 340 (1955)
172. Bloch, E. H., *Ergeb. Anat. u Entwicklungsgeschichte*, **35,** 1 (1956)
173. Thuránszky, K., *Acta Physiol. Acad. Sci. Hung.*, **9,** 44 (1956) Suppl.
174. Burton, A. C., *Ann. Rev. Physiol.*, **15,** 213 (1953)
175. Kovach, J., and Heinzen, B., *Acta Med. Scand.*, **154,** 111 (1956)
176. Klingenberg, H. G., *Arbeitsphysiol.*, **16,** 173 (1956)
177. Kramar, J., Meyers, V. W., and Simay-Kramar, M., *J. Lab. Clin. Med.*, **47,** 423 (1956)
178. Kramar, J., Meyers, V. W., Simay-Kramar, M., and Wilhelmj, C. M., Jr., *Am. J. Physiol.*, **184,** 640 (1956)
179. Goldman, R., and Bassett, S. H., *Circulation*, **12,** 630 (1955)
180. Albert, R. E., Smith, W. W., and Eichna, L. W., *Circulation*, **12,** 1047 (1955)
181. Geyer, G., Herbst, F. S. M., Thaler, H., and Lever, W. F., *J. Clin. Invest.*, **35** 281 (1956)

182. Gifford, R. W., Jr., Windesheim, J. H., Estes, J. E., Jr., and Roth, G. M., *Circulation*, **13**, 515 (1956)
183. Hope, A., and Verel, D., *Clin. Sci.*, **14**, 501 (1955)
184. Verel, D., Bury, J. D., and Hope, A., *Clin. Sci.*, **15**, 1 (1956)
185. Hanna, C. H., and Marshall, L. H., *Am. J. Physiol.*, **182**, 331 (1955)
186. Small, W. J., and Verloop, M. C., *J. Lab. Clin. Med.*, **47**, 255 (1956)
187. Huff, R. L., and Feller, D. D., *J. Clin. Invest.*, **35**, 1 (1956)
188. Karpeles, L. M., and Huff, R. L., *Circulation Research*, **3**, 483 (1955)
189. Lammerant, J., and de Schrevel, J., *Acta Cardiol.*, **10**, 250 (1955)
190. Gunton, R. W., and Paul, W., *J. Clin. Invest.*, **34**, 879 (1955)
191. Price, H. L., Helrich, M., and Conner, E. H., *J. Clin. Invest.*, **35**, 125 (1956)
192. Greisheimer, E. M., Ellis, D. W., Stewart, G., Makarenko, L., Thompson, K. T., and Oleksyshyn, N., *Am. J. Physiol.*, **182**, 145 (1955)
193. Zweifach, B. W., and Metz, D. B., *Am. J. Physiol.*, **182**, 155 (1955)
194. Akers, R. P., and Zweifach, B. W., *Am. J. Physiol.*, **183**, 529 (1955)
195. Crismon, J. M., and Dryer, R. L., *Am. J. Physiol.*, **185**, 113 (1956)
196. Wiedeman, M. P., *Circulation Research*, **3**, 618 (1955)
197. Bohr, D. F., Wolf, N. E., and Rondell, P. A., *Am. J. Physiol.*, **182**, 311 (1955)
198. Freed, S. C., and Rosenman, R. H., *Am. J. Physiol.*, **184**, 183 (1956)
199. von Euler, U. S., *Lancet*, **II**, 151 (1955)
200. von Euler, U. S., Luft, R., and Sundin, T., *Acta Physiol. Scand.*, **34**, 169 (1955)
201. Handler, P., *Am. J. Physiol.*, **184**, 400 (1956)
202. Schayer, R. W., Smiley, R. L., Davis, K. J., and Kobayashi, Y., *Am. J. Physiol.*, **182**, 285 (1955)
203. Brewster, W. R., Jr., Isaacs, J. P., Osgood, P. F., and King, T. L., *Circulation*, **13**, 1 (1956)
204. Boxill, G. C., and Brown, R. V., *J. Pharmacol. Exptl. Therap.*, **115**, 1 (1955)
205. Rosenman, R. H., Freed, S. C., and St. George, S., *Circulation Research*, **4**, 57 (1956)
206. Braun-Menéndez, E., and Penhos, J. C., *Compt. rend. soc. biol.*, **149**, 1676 (1955)
207. Braun-Menéndez, E., and Penhos, J. C., *Compt. rend. soc. biol.*, **149**, 1677 (1955)
208. Braun-Menéndez, E., and Penhos, J. C., *Compt. rend. soc. biol.*, **149**, 1661 (1955)
209. Braun-Menéndez, E., *Acta Cardiol.*, **10**, 323 (1955)
210. von Euler, U. S., and Pernow, B., *Acta Physiol. Scand.*, **36**, 265 (1956)
211. Page, I. H., and McCubbin, J. W., *Am. J. Physiol.*, **184**, 265 (1956)
212. Binet, L., and Burstein, M., *Compt. rend. soc. biol.*, **149**, 1860 (1955)
213. Schneider, J. A., and Rinehart, R. K., *Arch. intern. pharmacodynamie*, **105**, 253 (1956)
214. Loubatières, A., Sassine, A., and Mauche, J., *Compt. rend. soc. biol.*, **149**, 1634 (1955)
215. Weidmann, H., and Cerletti, A., *Helv. Physiol. et Pharmacol. Acta*, **13**, C38 (1955)
216. Taylor, R. D., and Page, I. H., *Am. J. Physiol.*, **183**, 12 (1955)
217. Brown, R. V., and Hilton, J. G., *Am. J. Physiol.*, **183**, 433 (1955)
218. Robertson, J. D., Swan, A. A. B., and Whitteridge, D., *J. Physiol.* (*London*), **131**, 463 (1956)
219. Nash, C. B., Davis, F., and Woodbury, R. A., *Am. J. Physiol.*, **185**, 107 (1956)
220. Granata, L., *Arch. intern. pharmacodynamie*, **102**, 391 (1955)

221. Heymans, C., and Delaunois, A. L., *Proc. Soc. Exptl. Biol. Med.*, **89**, 597 (1955)
222. Hilton, J. G., and Brown, R. V., *Am. J. Physiol.*, **183**, 206 (1955)
223. Hilton, J. G., and Brown, R. V., *Am. J. Physiol.*, **183**, 137 (1955)
224. Page, I. H., McCubbin, J. W., and Green, J. H., *Acta Cardiol.*, **10**, 576 (1955)
225. McCubbin, J. W., Green, J. H., and Page, I. H., *Circulation Research*, **4**, 205 (1956)
226. Navakatikyan, A. O., *Fiziol. Zhur., S.S.S.R.*, **42**, 88 (1956)
227. Douglas, W. W., and Schaumann, W., *J. Physiol. (London)*, **132**, 173 (1956)
228. Douglas, W. W., Ritchie, J. M., and Schaumann, W., *J. Physiol. (London)*, **132**, 187 (1956)
229. Douglas, W. W., and Ritchie, J. M., *J. Physiol. (London)*, **131**, 35P (1956)
230. Douglas, W. W., Ritchie, J. M., and Schaumann, W., *J. Physiol. (London)*, **131**, 36P (1956)
231. Peterson, L. H., *Circulation*, **2**, 351 (1950)
232. Boss, J., and Green, J. H., *Circulation Research*, **4**, 12 (1956)
233. Hubbard, S. J., *J. Physiol. (London)*, **132**, 23P (1956)
234. Henry, J. P., Gauer, O. H., and Sieker, H. O., *Circulation Research*, **4**, 85 (1956)
235. Matton, G., *Arch. intern. pharmacodynamie*, **103**, 13 (1955)
236. Witzleb, E., Bartels, H., Budde, H., and Mochizuki, M., *Pflügers, Arch. ges. Physiol.*, **261**, 211 (1955)
237. Mietkiewski, E., *Arch. intern. pharmacodynamie*, **104**, 373 (1956)
238. McCubbin, J. W., Green, J. H., Salmoiraghi, G. C., and Page, I. H., *J. Pharmacol. Exptl. Therap.*, **116**, 191 (1956)
239. Blood, F. R., Kosman, M. E., and D'Amour, F. E., *Am. J. Physiol.*, **182**, 180 (1955)
240. Lindgren, P., *Acta Physiol. Scand.*, **35**, Suppl. 121 (1955)
241. Cooper, K. E., Ferres, H. M., and Guttmann, L., *J. Physiol. (London)*, **132**, 11P (1956)
242. Dshavadyan, N. S., *Fiziol. Zhur., S.S.S.R.*, **41**, 512 (1955)
243. Oberholtzer, R. S. H., *Helv. Physiol. et Pharmacol. Acta*, **13**, 331 (1955)
244. Sigg, E., Ochs, S., and Gerard, R. W., *Am. J. Physiol.*, **183**, 419 (1955)
245. Arndt, T., Hauss, W. H., Hutwohl, G., and Kemper, F., *Z. Kreislaufforsch.*, **45**, 241 (1956)
246. Redgate, E. S., and Gellhorn, E., *Arch. intern. pharmacodynamie*, **105**, 193 (1956)
247. Redgate, E. S., and Gellhorn, E., *Arch. intern. pharmacodynamie*, **102**, 179 (1955)
248. Covian, M. R., and Houssay, H. E. J., *Circulation Research*, **3**, 459 (1955)
249. Cicardo, V. H., and Breiter, E., *Compt. rend. soc. biol.*, **149**, 1667 (1955)
250. Belenkij, G. S., *Fiziol. Zhur., S.S.S.R.*, **41**, 765 (1955)
251. Baranov, W. G., and Rozova, E. I., *Fiziol. Zhur., S.S.S.R.*, **42**, 203 (1956)
252. Prijma, G. Ya., *Fiziol. Zhur., S.S.S.R.*, **42**, 102 (1956)
253. Hilton, S. M., *J. Physiol. (London)*, **131**, 31P (1956)
254. Wakim, K. G., *Am. Heart J.*, **50**, 435 (1955)
255. Stein, D. H., and Hecht, H., *J. Clin. Invest.*, **34**, 867 (1955)
256. Maxwell, R. A., Plummer, A. J., and Osborne, N. W., *Circulation Research*, **4**, 276 (1956)
257. György, L., Zsigmond, E., and Pórszász, J., *Acta Physiol. Acad. Sci. Hung.*, **9**, 52 (1956) Suppl.
258. Malméjac, J., *J. Physiol. (London)*, **130**, 497 (1955)

259. Malmejac, J., Chardon, G., Neverre, G., and Gross, A., *Compt. rend. soc. biol.*, **149,** 679 (1955)
260. Brown, F. K., and Remington, J. W., *Am. J. Physiol.* **182,** 279 (1955)
261. Rodbard, S., and Katz, L. N., *Circulation*, **12,** 448 (1955)
262. Levy, M. N., Brind, S. H., and Brandlin, F. R., *Circulation Research*, **3,** 415 (1955)
263. Rodbard, S., and Stone W., *Circulation*, **12,** 883 (1955)
264. Cicardo, V. H., and Dutrey, D. E., *Arch. intern. Physiol.*, **63,** 190 (1955)
265. Holton, P., *J. Physiol.* (*London*), **131,** 176 (1956)
266. Capon, A., *Compt. rend. soc. biol.*, **149,** 611 (1955)
267. Emmelin, N., *Acta Physiol. Scand.*, **34,** 11 (1955)
268. Emmelin, N., *Acta Physiol. Scand.*, **34,** 22 (1955)
269. Emmelin, N., *Acta Physiol. Scand.*, **34,** 29 (1955)
270. Morgan, G. W., and Ferrante, W. R., *J. Acoust. Soc. Amer.*, **27,** 715 (1955)
271. Hardung, V., *Helv. Physiol. et Pharmacol. Acta*, **11,** 192 (1953)
272. Lawton, R. W., *Circulation Research*, **3,** 403 (1955)
273. Rushmer, R. F., *Am. J. Physiol.*, **183,** 545 (1955)
274. Lawton, R. W., and Greene, L. C., *U. S. Bur. Med. Surg.* (Project NM 001 100 315 #2 1956)
275. Schaffhauser, E., and Hardung, V., *Helv. Phys. Acta*, **28,** 303 (1955)
276. Peterson, L. H., and Shepard, R. B., *Surg. Clin. North Amer.*, **35,** 1613 (1955)
277. Kroeker, E. J., and Wood, E. H., *J. Appl. Physiol.*, **8,** 483 (1956)
278. Kroeker, E. J., and Wood, E. H., *Circulation Research*, **3,** 623 (1955)
279. Peterson, L. H., and Gerst, P. H., *J. Clin. Invest.*, **35,** 729 (1956)
280. Peterson, L. H., and Gerst, P. H., *Federation Proc.*, **51,** 144 (1956)
281. Wiggers, C. J., *Circulation Research*, **4,** 4 (1956)
282. Randall, J. E., and Stacy, R. W., *Am. J. Physiol.*, **185,** 351 (1956)
283. Porjé, I. G., *Scand. J. Lab. Clin. Invest.*, **7,** 79 (1955) Suppl. 20
284. Ronniger, R., *Arch. Kreislaufforsch.*, **21,** 127 (1954)
285. Lindner, A., and Ronniger, R., *Arch. Kreislaufforsch.*, **22,** 72 (1955)
286. Ronniger, R., *Arch. Kreislaufforsch.*, **22,** 332 (1955)
287. McDonald, D. A., *J. Physiol.* (*London*), **127,** 533 (1955)
288. Lessen, M., and Peterson, L. H., *J. Physiol.* (*London*), **130,** 18P (1955)
289. Guyton, A. C., and Greganti, F. P., *Am. J. Physiol.*, **185,** 137 (1956)
290. Guyton, A. C., Armstrong, G. G., and Chipley, P. L., *Am. J. Physiol.*, **184,** 253 (1956)
291. Salisbury, P. F., Rieben, A., Himelson, A., and Johnson, C. W., *Am. J. Physiol.*, **183,** 513 (1955)
292. Freis, E. D., Broida, H. P., Hufnagel, C. A., and Rose, J. C., *Am. J. Physiol.*, **182,** 191 (1955)
293. Monod, R., and Zacouto, F., *Compt. rend. soc. biol.*, **149,** 1380 (1955)
294. Mechelke, K., Nusser, E., and Hey, W., *Pflügers Arch. ges. Physiol.*, **261,** 527 (1955)
295. Braunwald, E., Fishman, A. P., and Cournand, A., *Circulation Research*, **4,** 100 (1956)
296. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. J., *Circulation*, **12,** 69 (1955)

297. Jungmann, H., and Erdmann, W. D., *Z. Kreislaufforsch.*, **45,** 252 (1956)
298. Heyman, F., *Acta Med. Scand.*, **152,** 91 (1955)
299. German, W. J., and Black, S. P. W., *Circulation Research* **3,** 463 (1955)
300. Fowler, N. O., and Mannix, E. P., *J. Clin. Invest.*, **34,** 1242 (1955)
301. Alexander, R. S., *Circulation Research*, **4,** 49 (1956)
302. Bovet, D., Gatti, G. L., and Virno, M., *Helv. Physiol. et Pharmacol. Acta*, **13,** C6 (1955)
303. Luthy, E., and Stucki, P., *Helv. Physiol. et Pharmacol. Acta*, **13,** C24 (1955)
304. Wood, J. E., Litter, J., and Wilkins, R. W., *Circulation*, **13,** 524 (1956)
305. Wood, J. E., Litter, J., and Friedman, I. H., *J. Clin. Invest.*, **34,** 972 (1955)
306. Altmann, R., *Klin. Wochschr.*, **33,** 1109 (1955)
307. Gauer, O. H., and Henry, J. P., *Klin. Wochschr.*, **34,** 356 (1956)
308. Stacy, R. W., Williams, D. T., Worden, R. E., and McMorris, R. O., *Essentials of Biological and Medical Physics* (McGraw-Hill Book Co., Inc., New York, N. Y., 586 pp., 1955)
309. Wezler, K., *Klin. Wochschr.*, **33,** 1111 (1955)
310. Jeffords, J. V., and Knisely, M. H., *Angiology*, **7,** 105 (1956)
311. Madow, B., and Bloch, E. H., *Angiology*, **7,** 1 (1956)
312. Reis, A., and Miller, J., *Klin. Wochschr.*, **34,** 197 (1956)
313. Krosch, H., and Heidelmann, G., *Klin. Wochschr.*, **33,** 947 (1955)
314. Davey, D. A., *J. Physiol.* (*London*), **132,** 1P (1956)
315. Alekseyev, W. A., *Fisiol. Zhur. S.S.S.R.*, **42,** 430 (1956)
316. Watts, D. T., *Am. J. Physiol.*, **184,** 271 (1956)
317. Frank, H. A., Frank, E. D., Korman, H., Macchi, I. A., and Hechter, O., *Am. J. Physiol.*, **182,** 24 (1955)
318. Frank, E. D., Kaufman, D., Korman, H., Schweinburg, F., Frank, H. A., and Fine, J., *Am. J. Physiol.*, **182,** 166 (1955)
319. Crowell, J. W., and Read, W. L., *Am. J. Physiol.*, **183,** 565 (1955)
320. Gauer, O. H., Henry, J. P., and Sieker, H. O., *Circulation Research*, **4,** 79 (1956)
321. Wadsworth, G. R., *J. Physiol.* (*London*), **129,** 583 (1955)
322. Fowler, N. O., Franch, R. H., and Bloom, W. L., *Circulation Research*, **4,** 319 (1956)
323. Millican, R. C., *Am. J. Physiol.*, **183,** 187 (1955)
324. Koletsky, S., and Klein, D. E., *Am. J. Physiol.*, **182,** 439 (1955)
325. Brehm, H., *Z. Kreislaufforsch.*, **44,** 471 (1955)
326. Schreiner, B., *Z. Kreislaufforsch.*, **44,** 806 (1955)
327. Lewis, D. H., *J. Aviation Med.*, **26,** 479 (1955)
328. Bondurant, S., and Hickam, J. B., *J. Clin. Invest.*, **35,** 692 (1956)
329. Hitchcock, F. A., and Kemph, J., *J. Aviation Med.*, **26,** 289 (1955)
330. Vavala, D. A., *J. Aviation Med.*, **26,** 230 (1955)
331. Haymaker, W., Johnston, A. D., and Downey, V. M., *J. Aviation Med.*, **27,** 2 (1956)
332. Monge, C. C., Cazorla, A. T., Whittenbury, G. M., Sakata, Y. B., and Rizo-Patron, C., *Acta Physiol. Latinoamer.*, **5,** 198 (1955)
333. Becker, E. L., Cooper, R. G., and Hataway, G. D., *J. Appl. Physiol.*, **8,** 166 (1955)
334. Handel, M., Weisz, K., and Pataki, J., *Acta Physiol. Acad. Sci. Hung.*, **8,** 247 (1955)
335. Nahas, G. G., and L'Allemand, H., *J. Appl. Physiol.*, **8,** 468 (1956)

336. Heath, C., and Brown, E. B., Jr., *J. Appl. Physiol.*, **8**, 495 (1956)
337. Kleinerman, J., and Sancetta, S. N., *J. Clin. Invest.*, **34**, 945 (1955)
338. Asmussen, E., and Nielson, N., *Physiol. Revs.*, **35**, 778 (1955)
339. Bishop, J. M., Donald, K. W., and Wade, O. L., *Clin. Sci.*, **14**, 329 (1955)
340. Bader, R. A., Bader, M. E., Rose, D. J., and Braunwald, E., *J. Clin. Invest.*, **34**, 1524 (1955)
341. Steinmann, S., Jaggi, A., and Widmer, J., *Cardiologia*, **27**, 223 (1955)
342. Lehmann, G., and Tamm, J., *Arb. physiol.*, **16**, 217 (1956)
343. Benelli, C., Faure, J., and Rougier, G., *Compt. rend. soc. biol.*, **149**, 1256 (1955)
344. Benelli, C., Faure, J., and Rougier, G., *Compt. rend. soc. biol.*, **149**, 1269 (1955)
345. Salpeter, M. M., *Am. J. Physiol.*, **182**, 177 (1955)
346. Fregley, M. J., *Am. J. Physiol.*, **182**, 139 (1955)
347. Fregley, M. J., Yates, F. E., and Landis, E. M., *Proc. Soc. Exptl. Biol. Med.*, **90**, 695 (1955)
348. Mott, J. C., *J. Physiol.* (*London*), **130**, 51P (1955)
349. Kreuziger, H., Kemper, F., and Heinecker, R., *Z. Kreislaufforsch.*, **45**, 167 (1956)
350. Taubenhaus, M., Eisenstein, B., and Pick, A., *Circulation*, **12**, 903 (1955)
351. Bunin, K. W., *Fiziol. Zhur. S.S.S.R.*, **42**, 357 (1956)
352. Brandfonbrener, M., Landowne, M., and Shock, N. W., *Circulation*, **12**, 557 (1955)
353. Landowne, M., Brandfonbrener, M., and Shock, N. W., *Circulation*, **12**, 567 (1955)
354. Ringer, R. K., Weiss, H. S., and Sturkie, P. D., *Am. J. Physiol.*, **183**, 141 (1956)
355. Wessler, S., and Morris, L. E., *Circulation*, **12**, 553 (1955)
356. Davis, O. F., Oester, Y. T., and Friedman, B., *Circulation Research*, **3**, 374 (1955)
357. Judson, W. E., Hatcher, J. D., and Wilkins, R. W., *Circulation*, **11**, 889 (1955)
358. Horvath, S. M., Allbaugh, E., and Hamilton, L., *Am. J. Physiol.*, **183**, 193 (1955)
359. Dow, P., *Physiol. Revs.*, **36**, 77 (1956)
360. Shepherd, J. T., Bowers, D., and Wood, E. H., *J. Appl. Physiol.*, **7**, 629 (1955)
361. Grace, J. B., Crowley, W. P., Fox, I. J., and Wood, E. H., *J. Clin. Invest.*, **34**, 936 (1955)
362. Burger, H. C., Van der Feer, Y., and Douma, J. H., *Acta Cardiol.*, **11**, 1 (1956)
363. Comet, S., and Lagerlof, H. O., *Acta Physiol. Scand.*, **36**, 337 (1956)
364. Comet, S., and Lagerlof, H. O., *Acta Physiol. Scand.*, **36**, 348 (1956)
365. Salonikides, N., *Acta Cardiol.*, **10**, 287 (1956)
366. Lacy, W. W., Ugaz, C., and Newman, E. V., *Circulation Research*, **3**, 570 (1955)
367. Theilen, E. O., Gregg, D. E., Paul, N. H., and Gilford, S. R., *J. Appl. Physiol.*, **8**, 330 (1955)
368. Falholt, W., and Kaiser, E., *Circulation Research*, **3**, 469 (1955)
369. Huff, R. L., Feller, D. D., Judd, O. J., and Bogardus, G. N., *Circulation Research*, **3**, 564 (1955)
370. Groom, A. C., and Rowlands, S., J. *Physiol.* (*London*), **132**, 5P (1956)
371. Kaufmann, G., and Hegglin, R., *Cardiol.*, **28**, 207 (1956)
372. Clausen, D. F., and Lifson, N., *Proc. Soc. Exptl. Biol. Med.*, **91**, 11 (1956)
373. Grossman, J., Rubler, S., Horowitz, H. B., and Weston, R. E., *J. Clin. Invest.*, **34**, 937 (1955)
374. Sapirstein, L. A., and Ogden, E., *Circulation Research*, **4**, 245 (1956)
375. Aschoff, J., and Wever, R., *Pflügers Arch. ges. Physiol.*, **262**, 133 (1956)

376. Wever, R., and Aschoff, J., *Pflügers Arch. ges. Physiol.*, **262,** 152 (1956)
377. Baumgartner, G., Grupp, G., and Janssen, S., *Pflügers Arch. ges. Physiol.*, **261,** 557 (1955)
378. Anschutz, F., Drube, H. C., and Seusing, J., *Klin. Wochschr.*, **34,** 277 (1956)
379. Schroeder, W., *Pflügers Arch. ges. Physiol.*, **261,** 507 (1955)
380. Starr, I., *J. Appl. Physiol.*, **8,** 315 (1955)
381. Starr, I., Askovitz, S. I., Feder, W., and Schild, A., *Circulation*, **12,** 1005 (1955)
382. Starr, I., *Circulation*, **11,** 914 (1955)
383. Starr, I., Pederson, E., and Corbascio, A. N., *Circulation*, **12,** 588 (1955)
384. Henderson, C. B., *Circulation*, **12,** 858 (1955)
385. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12,** 577 (1955)
386. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12,** 845 (1955)
387. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12,** 1022 (1955)
388. Reubi, F., and Schmid, A., *Cardiol.*, **28,** 197 (1956)
389. Polzer, K., and Schuhfried, F., *Z. Kreislaufforsch.*, **44,** 631 (1955)
390. Brombacher, W. G., and Lashof, T. W., *U. S. Nat. Bur. Standards* (Circular 558, 1955)
391. Thomas, J. G., *J. Physiol.* (*London*), **129,** 75P (1955)
392. Still, J. W., Pradhan, S. N., and Whitcomb, E. R., *J. Appl. Physiol.*, **8,** 575 (1956)
393. Ordynskij, S. I., and Zubchenkov, W. I., *Fiziol. Zhur. S.S.S.R.*, **41,** 695 (1955)
394. Flath, R., and Landowne, M., *J. Appl. Physiol.*, **8,** 220 (1955)
395. Gauer, O. H., and Sieker, H. O., *Circulation Research*, **4,** 74 (1956)
396. Hale, J. F., McDonald, D. A., Taylor, M. G., and Womersley, J. R., *J. Physiol.* (*London*), **129,** 27P (1955)
397. Radner, S., *Acta Med. Scand.*, **152,** 1 (1955)
398. Dahlback, O., and Radner, S., *Acta Chir. Scand.*, **109,** 310 (1955)
399. Radner, S., Edler, I., and Gustafson, A., *Acta Med. Scand.*, **152,** 271 (1955)
400. Radner, S., *Acta Med. Scand.*, **152,** 413 (1955)
401. Stauffer, H. M., Oppenheimer, M. J., Stewart, G. H., and Lynch, P. R., *J. Appl. Physiol.*, **8,** 343 (1955)
402. Dotter, C. T., *Circulation*, **12,** 1034 (1955)
403. de Sousa, A., *Compt. rend. soc. biol.*, **149,** 435 (1955)
404. Drenckhahn, F. O., *Pflügers Arch. ges. Physiol.*, **262,** 169 (1956)
405. Egdahl, R. H., *Am. J. Physiol.*, **182,** 454 (1955)
406. Kilb, H., and Stampfli, R., *Helv. Physiol. et Pharmacol. Acta*, **13,** 191 (1955)
407. Lakomkin, A. I., *Fiziol. Zhur. S.S.S.R.*, **41,** 832 (1955)
408. Kjelberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B., *Diagnosis of Congenital Heart Disease* (The Year Book Publishers, Inc., Chicago, Ill., 649 pp., 1955)
409. Brecher, G. R., *Venous Return* (Greene and Stratton, Inc., New York, N. Y., 148 pp., 1956)

EFFECTS OF RADIATION ON MAMMALS[1,2,3]

V. P. Bond and E. P. Cronkite
Medical Department, Brookhaven National Laboratory, Upton, Long Island, New York

Introduction

Since the last review in this journal (2) covering the subjects to be reviewed here ("Modification of Radiation Effects by Chemical Means, and Post-Irradiation Restoration of Tissues"), a large number of pertinent publications have appeared. Some degree of selection has been necessary, and many papers have not been discussed in the detail they deserve because of space limitations. A number of articles with interesting titles, published in foreign journals, were not available for review. The problems concerned with the physical and chemical effects of radiation on pure and simplified systems in general are not considered, except where they appear to apply directly to mammalian effects. Reports from the Atomic Energy Commission contract laboratories and the Department of Defense are listed only when they bear heavily upon one of the major topics under review, since most are eventually published in the open literature.

Modification of Radiation Effects by Chemical Means

General considerations.—This subject in general has been covered well in a number of recent articles, books, and reviews (1 to 16). Collections of pertinent papers presented at the International Conference on the Peaceful Uses of Atomic Energy in Geneva, August, 1955 (17), and at the Fourth International Conference on Radiobiology, Cambridge, August, 1955 (18), are available. Certain aspects of the problem which are of general interest

[1] This survey covers the period of June, 1953, to July, 1956. The field of the effects of radiation on mammals has grown too extensively to allow effective coverage in a single chapter. The present chapter deals only with "Modification of Radiation Effects by Chemical Means and with Post-Irradiation Restoration of Tissues." A previous chapter by the same authors (1) dealt with "Relative Biological Effectiveness, Cataractogenesis, Carcinogenesis, Physiological and Histological Effects, Endocrines, Direct and Abscopal Effects, Embryology, Development and Mamallian Genetics, Biochemical Effects and Resistance to Infection."

[2] The following abbreviations have been used in this chapter: ACTH (adrenocorticotropin); RNA (ribonucleonic acid); DNA (deoxyribonucleic acid); MCA (methylcholanthrene); ATP (adenosinetriphosphate); TSH (thyroid-stimulating hormone); G.I. (gastrointestinal); WBR (whole body radiation); DPN (diphosphopyridine nucleotide); RES (reticuloendothelial system); STH (somatotrophic hormone); A.G. (albumin-globulin); PAPP (para-amino propriophenone); MEA (beta mercaptoethylamine, cysteamine); PMA (polymethacrylic acid); BAL (dimercaptopropanol).

[3] Leukemoid reaction induced by transplantation of a squamous cell carcinoma.

will be reviewed here. Since the demonstrations of the protective effect of cysteine and glutathione against radiation damage, a large number of protective substances have been added, and the list of preparations for which some protective action is claimed presents a formidable array. Additional information has been obtained on the results of irradiating biological materials in various gases (varying oxygen tension, nitrogen, hydrogen). Test systems in which protection has been demonstrated range from simple chemical systems, through macromolecular, unicellular, cellular, and complex mammalian structures. The wide variation in degree of protective effect depending on the biological endpoint studied has become more and more appreciated. The importance of attempting to protect against genetic effects has been pointed out, and the presence of serious late complications in protected survivors has been brought to attention (most protection in mammals is demonstrated on the basis of 30-day survival). The efficacy of combining various pre-protective agents, and pre-protective with post-exposure restorative agents has been demonstrated. It has been possible to triple the 30-day LD_{50} for mice, using a combination of agents. The translation of esoteric protective procedures in the laboratory to potentially practical approaches for man has received attention, and some protective procedures, as well as intensifying agents, have been tried in clinical radiotherapy. Although a great deal of information has been collected, and much thought has been given to the mechanism of action in protective procedures (closely linked with the mechanism of action of ionizing radiations), there seems to have been no major break through in these areas. There would seem to be little point in reiterating the basic theories on mechanism of action of ionizing radiation, which are covered in previous review articles (1 to 16). The protective effects of antibiotics were considered in the previous review by the same authors (1).

Mechanisms of action.—Butler (19) has surveyed the status of knowledge in radiobiology, and emphasizes the need for information on the actual structural components of the cell before radical progress is probable. Alexander (20) has developed a physicochemical model system using PMA for the testing of the protective action of chemical compounds against the effects of radiation. This system may have some practical usefulness, since there apparently has been a good parallelism between the protective effect in the PMA system and *in vivo* results with mice (21). The physicochemical model system depends upon the degradation of PMA solutions by radiation. Apparently, the degradation results from the combination of HO_2 free radicals with PMA, forming an unstable intermediate as follows:

$$RH + HO_2 \rightarrow H_2O + RO$$
$$R = PMA$$

RO is unstable and decomposes. Protective reagents could either compete with the polymer for the HO_2 radical or combine with the unstable intermediate and form a stable compound.

The above problem and its relation to transfer reactions and the entire problem of the mechanism of protection of chemical compounds was discussed by Alexander *et al.* (20, 22). They emphasize the importance of the SH and NH_2 groups, as have Doherty & Burnett (23), and it can be said in general that SH and NH_2 groups have considerable protective action when present on the same molecule. However, some SH compounds, e.g., ergothioneine, confer no protection. These workers (20, 22) believe that most of the chemical protectors that are effective *in vivo* also act by competition for HO_2 radicals which are produced by x-rays only in the presence of oxygen. For this reason, these authors disagree with those who feel that chemical protectors act by producing temporary tissue anoxia (24, 25, 26). Salerno *et al.* (25, 26) found markedly reduced oxygen tension in the tissues of animals given cysteine in protective amounts, and found that oxygen under a pressure of 60 lbs. per sq. in. abolished the protective effect of cysteine, PAPP, and MEA in rats. This, with other evidence presented, would indicate that these agents may act to a large degree by virtue of their hypoxia-producing effects. van Bekkum & Cohen (27) and van Bekkum & de Groot (28) have tested a variety of chemical protectors in the mouse, and *in vitro* using a suspension of isolated rat thymocytes. With several compounds excellent protection was obtained in the mouse; none in the *in vitro* system. The authors feel these results cannot be readily explained by postulating interaction between the protector and the radicals during irradiation; rather the drugs must act *in vivo* by way of some systematic effects, e.g., on the vascular or respiratory systems, with possibly a hypoxic state in some tissues. Gray (29) has undertaken a series of experiments to determine the effect of protective agents on dissolved oxygen under conditions used in radiobiological experiments.

Shapiro, Eldjarn & Pihl (30 to 33), in a series of investigations, have shown that cysteamine and cystamine show not only differential concentration in various tissues, but that proteins within the cells have differential affinities for the compounds. They feel the protective action of these compounds may involve a protein-cysteamine disulphide linkage, resulting in partial protection of the radiochemically sensitive protein-SH groups. Thus protective action may result by specific alteration of the nature of the biological target, and the degree of protective action of an SH compound will depend on its ability to penetrate cell membranes, its rate of intracellular oxidation to the disulphide form, and its affinity for the protein-SH groups. Langendorf *et al.* (34) has discussed the relationship of the protective action of cysteine and glutathione to the redox potentials of these compounds.

Devik (35) found D-cysteine and L-cysteine to have the same degree of effectiveness, and interpreted this to indicate that the protection may be radiochemical, rather than biological in nature. Patt *et al.* (36) have reported a systematic dose reduction by cysteine in tissues studied, perhaps indicating a primary chemical mode of action. However, the long exposure period of 90 minutes used in their studies permitted the cysteine to be largely metab-

olized and, therefore, the experiments are difficult to interpret. The concept of dose reduction is compatible with the data under conditions where the agent reached the tissue under study. However, as discussed by Cronkite *et al.* (12), there are systems where the concept does not apply, perhaps because of a failure of the agent to reach the tissue in question. Hirsch (37) studied the formation of melanin from dopa and concludes that while the auto-oxidative process is metal-catalyzed, the radiation-induced process is the result of direct interaction of the radiation-produced oxidants. A tissue component strongly inhibiting auto-oxidation did not inhibit the radiation-induced reaction. It appears that x-ray induced melanin formation does not result from hydrogen peroxide, since this chemical does not oxidize dopa. The system is proposed to screen possible radioprotective agents. The possibility that pre-protective agents may act by protecting a biological factor, which in turn effects recovery will be discussed later.

Clark & Herr (38) found that *Habrobracon* irradiated in nitrogen, carbon dioxide or hydrogen were afforded protection over those irradiated in oxygen in air, a nd conclude from the data that no clear relationship exists between x-radiation damage and oxygen poisoning in the system studied.

Although logical explanations for the ability to protect or to not protect are given by various investigators, the systems involved in integrated plant and mammalian systems are so complex that it is difficult, if not impossible at this time, to correlate meaningfully *in vitro* protection of a relatively simple chemical system with *in vivo* protection. It cannot be said at this time, in complex systems, whether the agent injected has changed the biological substrate to a more radioresistant state, whether actual competition for free radicals is underway, or whether production of peroxides, etc., has been diminished by an oxygen deficit. It is of considerable importance to settle this question (27). If the mechanism of action is via an oxygen deficit, the limit of protection is determined by the limit of hypoxia that will sustain life in the organism, and the search is limited to methods to produce general, or preferably localized, tissue anoxia. If protection depends on interaction between the protector and the biological material or the radicals present in the irradiated cell, the degree of effect will depend on the specific affinity of the protector for substances in the cell, and on the concentration of the protector in the cell. The limits of maximal protection on this basis are not apparent as yet. For a more detailed discussion of possible mechanisms of protection by chemical protectors *in vitro* and *in vivo*, one is referred to the original articles cited.

SH compounds.—A vast amount of work has been done on the protective action of various SH-containing compounds. Doherty & Burnett (23) have studied the effect of altering the MEA molecule on the relative protective action. Replacement of the sulfhydryl group with the isothiuronium group resulted in a compound that appeared to have increased chemical stability and to afford protection in mice with chemical doses well below the toxic level. A free amino group, in addition to the SH or isothiuronium groups, was found necessary for protection.

Numerous anatomical, physiological, and biochemical studies on the influence of protective agents on mammals have been reported. Following protection by sulfhydryl compounds, cyanide, and anoxia, it has been observed that the early lesions in the lymphoid tissues, spleen, bone marrow, intestinal epithelium, and gonads were similar to the control irradiated animals (39 to 43). However, by the sixth to seventh day, the adrenal cortex and liver of the cyanide pre-tested animals were believed to show less damage (39). Baldini & Ferri (44) found no evidence that the protection afforded to rats by cystamine and cysteamine was mediated through the pituitary or adrenal. Bacq *et al.* (45) found that it was not necessary that the adrenals be intact in order for cysteamine to be effective. They claim two periods of adrenal hyperactivity following irradiation (45, 46), one occurring at about one to two hours after irradiation with recovery by 24 hours, and another on the 2nd or 3rd day, reaching a peak on the fourth day. At x-ray and cysteine doses that allow 90 per cent survival, the adrenal hyperactivity is suppressed during the second period, unaffected during the first. Fischer (47) irradiated rats with and without barbiturates, and found that the anaesthesia abolished the early fall in adrenal cholesterol resulting from the irradiation, but did not affect the fall in ascorbic acid content. Since barbiturates afford essentially no protection against x-ray mortality, and cysteamine affords marked protection, it is concluded that the early adrenal reaction is of little importance in radiation deaths. Maisin feels that MEA protects against intestinal and bone marrow damage (48, 49), but not against testicular atrophy (48).

Jennings & Tessmer (50) studied the protective action of glutathione against the lethal effects of total body irradiation in mice and feel their data support the concept that the primary action of glutathione may reside in the spleen, possibly by protection of undifferentiated hemopoietic cells in that organ. Maisin feels that MEA tagged with radioactive sulfur is fixed in larger quantities in "protected" organs; less in nonprotected. Weight loss in mice for the first two days in SH-treated and control animals was the same, but thereafter, weight gain was rapid in the protected animals and loss continued to death in the controls (51). In rats protected by SH there was less weight loss (52). The most striking and uniform phenomenon was the early and diffuse regeneration, particularly of hemopoietic tissues throughout the body of pretreated animals. The similarity of regeneration of hemopoietic tissues in the SH-protected mice and spleen protected mice led one of us (E.P.C.) to postulate that chemical protection was based on protection of regeneration factors (cellular or humoral), a subject that was discussed by Alexander, Bacq and associates (3, 15, 21). Attractive as the hypothesis may be, perhaps it is an oversimplification. The radio-protectors are not uniformly distributed in all tissues and do not protect against all biological effects; for example, against testicular weight loss (49) and genetic damage (53) in mice. The bulk of dividing cells in hematopoietic tissue are relatively immature. As new cell production stops, they mature and pass out into the blood stream. The cells from which regeneration takes place in hematopoietic tissues are

immature and few in number. They may concentrate the protective agent and thus be protected; however, such protection would not be evident grossly because of the small number of cells involved. The protection in these immature cells may manifest itself with a diminution in the prolongation of the intermitotic period; thus, an earlier return of mitosis and active regeneration would be seen. The formative cells may be directly protected, but this would not be manifested by a lesser degree of atrophy of radiosensitive tissues. In fact, Williams (54) has produced evidence that there was an earlier return of mitosis in the G.I. tract following glutathione administration. Desaive & Varetto-Denoël (55), studying the mitosis of epithelial cells of the small intestine, claim that cysteamine protects the small intestine against 500 r of x-radiation applied locally. It is not necessary to invoke the concept of protection of regeneration factors of a noncellular nature. At the present time, we are inclined to think that it is only necessary for the chemical protector to reach the formative cells to provide protection and that it is not necessary to consider remote organs as supplying a "regenerative force" as proposed by Alexander *et al.* (21).

Maisin and associates (56, 57) have reported that cysteamine protection was additive to shielding, particularly of the liver region. However, these studies are difficult to interpret, since external shields over the hepatic area will shield portions of bowel and bone marrow, organs also known to protect against radiation injury. These authors claim that MEA affords protection against both the intestinal and bone marrow syndromes of acute total body radiation, that it is effective orally (58), and that it protects against nitrogen mustard toxicity (59). Patt has pointed out that the increased effectiveness of MEA over other protective SH compounds is offset by its greater toxicity (2). Cysteamine protection and its possible relation to coenzyme A has been discussed at length by Bacq *et al.* (3, 15, 21, 60).

Rugh & Clugston (61) have shown that cysteamine given before irradiation prolonged survival time of mice given 66,000 r at 1500 r/min. If given after irradiation with these high doses, the animals died more quickly, indicating a synergism.

Gros, Mandel & Rodesch (62) have shown that DNA and RNA of spleen of rats diminished in parallel in control and cysteamine-treated rats for one to two days, but by the fourth day, the treated rats had a much higher nucleic acid content. Fischer (63) stated that MEA prevented the accumulation of glycogen in the liver of fasting rats eight hours after irradiation. Höhne *et al.* (64) could demonstrate no effect of MEA on the electrophoretic pattern of serum proteins in the irradiated rat. Peterson *et al.* (65) found that the protective capacities (against mortality) of PAPP, cysteine, and MEA coincided with their ability to diminish the increased phosphatase activity noted in the spleen and thymus of irradiated rats. The results suggested a similarity in action of the three protective agents.

Various other aspects of sulfhydryl protection have been reported, e.g., effects of cysteamine on young irradiated mice by Nelson (66), cysteamine

protection of cornea from beta radiation by McDonald (67), and the prevention of decrease in spleen succinoxidase by pre- and post-radiation injection of cysteamine by Fischer *et al.* (68). Protection by thiourea (69) and lack of protection by allyl thiourea (70) were reported. Tentative explanations for failure and ability to protect were offered by Alexander *et al.* (21). Odeblad (71) found that BAL in a single injection before irradiation did not protect the ovaries from WBR (400 to 600 r), but afforded significant protection against the effects of P^{32} if administered prior to, and repeatedly after injection of the isotope.

Rugh & Clugston (72) were able to demonstrate protection of the fetus by administration of beta-mercaptoethylamine to the mother prior to irradiation, and similar results were claimed by Maisin *et al.* (48). Hofman (73) used a photoelectric method to evaluate erythema of the rat tail, and claims that using subcutaneous injection he could demonstrate that cysteine and cystine both afforded protection by local action.

Several authors have reported that cysteamine affords protection against the undesirable side effects (nausea, vomiting, diarrhea) observed in clinical radiotherapy, even when given *after* exposure (74 to 76). Baldini & Ferri (76) report that cysteamine results in increased white blood count at the end of treatment. Bacq (74) calls the post-irradiation protection "therapeutic or restorative," as opposed to "protective" when the drug is administered before irradiation. The mechanism of the possible protective action when the drug is given after irradiation is not clear. Court-Brown (77) in a small but carefully controlled series, was unable to demonstrate any effect of cysteamine, given before or after therapy, on the incidence of clinical radiation sickness. Similarly, Silverman *et al.* (78) could demonstrate no effect of pyridoxine or dramamine over a placebo, and Sicher (79) found no benefit to be derived from the use of ACTH. Brohult & Holmberg (80) have used batyl alcohol (3,[octadecyloxy]-1,2-propanediol) in the therapy of patients with leukopenia induced by chronic irradiation. Presumably there was a response, but the report was difficult to interpret, since inadequate data were presented.

Other chemical protective agents.—In addition to the sulfhydryl-amine series of compounds that conferred protection, numerous studies have been reported on the protective effects of other biochemical and inorganic compounds. Methyl and ethyl linoleate and fat in the diet has been reported to confer protection (81, 82, 83). Lacassagne *et al.* (84) have presented convincing evidence that phenolic and naphtholic derivatives containing long-chain fatty acids, as well as glucosamine, will confer considerable protection, providing they are administered to mice shortly before irradiation. Duplan & Rosenberg (85) have reported protection using glucosamine. Langendorf & Koch (86) tested a series of amines for protective effect against radiation, and found only tryptamine to be effective. Oxypolygelatin, a plasma expander, given daily to irradiated rabbits was detrimental, producing some deaths shortly after irradiation and others at a later period (87). The early deaths were believed to be due to hypervolemic cardiac failure, and later

deaths were accompanied by multiple lesions, edema, hemorrhage, infarcts and tubular degeneration.

Stroud *et al.* (88) reported experiments on protection of mice by pre-irradiation administration of homologous or heterologous serum or plasma. The protective effect was associated with Cohn fractions II and III. Additivity of effect to maximal cysteine effect suggested different pathways of action. The effect was not due to SH content. Post-radiation protection was absent. A material with similar effect was obtained by perfusion of spleens from irradiated dogs in which the spleen was shielded, but not from normal spleens of non-irradiated dogs. Rowen *et al.* (89) obtained 82 per cent mortality in mice given H. pertussis vaccine intraperitoneally 5 days prior to exposure to 300 r of x-radiation, as opposed to 12 per cent mortality in x-irradiated control. The increased sensitivity is comparable to that shown by the pertussis-vaccinated mouse to histamine and anaphylaxis. Hydrocortisone did not alter the increased sensitivity to radiation. Yaoi & Kimura (90) found that serial subcutaneous injection of purified vaccine lymph *after* x-irradiation conferred protection against irradiation mortality and weight loss. The authors feel the protection conferred is greater than that obtained with cow skin protein without virus, or from spleen homogenates; however, this conclusion is not shown definitely in the data presented.

In an extension of studies on "protective effect" of yellow bone marrow extracts against myeloid depression, batyl alcohol, a constituent of yellow bone marrow, was investigated in radiation injury (91, 92). In unconfirmed experiments, Edlund has found that mice treated with batyl alcohol after 750 r WBR had a greater survival rate. Becker & Kirchberg (93) reported no protective action of Periston *N*. Maurer (94) found no protective effect of adenosine triphosphate given intravenously to six rabbits prior to irradiation. The ATP blood levels remained high during, and for five days or less following irradiation. Survival time was shortened by the treatment. Laurell & Philipson (95) obtained only erratic results treating irradiated mice with a dextran sulfuric acid (claimed to stimulate hemopoiesis), and pyrogen *P.*, prepared from *Pseudomonas pyocyaneus.*

Ganglionic blocking agents were found not to influence the course of radiation injury in mice (96), whereas cholinergic blocking drugs exerted some beneficial effects (97, 98). Barlow & Sellers (99) gave growth hormone after x-irradiation to rats, and could not demonstrate a beneficial effect on survival rate, organ weight loss, or histological picture. Essentially similar results were reported by Betz (100) and by Hoene *et al.* (101). One previous report had indicated increased survival with GH; another had observed no such effect. Oxytocin has been reported to protect mice if given before irradiation (102). The effect of hormones on radiation damage has been discussed by other authors (103, 104). Mucke *et al.* (105) claim some protection against radiation-induced leukopenia and erythropenia in guinea pigs by means of folic acid and Vitamin B_{12}, particularly when administered prior to irradiation. Bond *et al.* (106) demonstrated no effect of irradiation on

the Vitamin B_{12} content of rat tissues. Water soluble Vitamin E has been shown not to prevent the harmful effects of radiation in mice. In fact, after the higher doses of the vitamin, survival time was shortened (107).

Studies on citrovorum factor and of rutin and bioflavonoids in radiation injury have continued. Buchanan *et al.* (108) have shown that citrovorum factor did not influence leukopoiesis in the irradiated rat. Cohen (109) and Arons *et al.* (110, 111, 112) reported beneficial effects on radiation injury, particularly in respect to minimizing capillary injury during radiotherapy. Although the data conflicted with previous reports (2, 3, 6, 11) on the effectiveness of this series of compounds in radiation injury, the results suggested, but did not prove, that these compounds may have some usefulness. It would be interesting to know if the flavonoids will influence the degradation of PMA in Alexander's model system (20, 21). Andrews & Liljegren (113) found that morphine or Nalorphine conferred slight protection against radiation mortality if administered prior to exposure. Burdick (114) and Gros & Comsa (115) reported protection using anesthetic agents. Shapiro *et al.* (116) demonstrated protective action of synestrol and diethylstilbestrol, and found that progesterone did not diminish the protection afforded by the estrogens.

Parr *et al.* (117) have continued studies on cobalt modification of radiation injury. It was found that there was a specific time interval during which the cobalt had to be in the diet in order to exert the beneficial effect. It was proposed by these workers that the greatest protection occurred when the cobalt stimulus to blood formation was being exercised and was not present after a cobalt polycythemia had been induced. Blount (118), on the theory that administered magnesium reduces body temperature, in itself protective, administered 15 mg. of $MgSO_4$ to mice prior to exposure and obtained 23 per cent mortality vs. 74 per cent in the control groups. The following have been shown to afford some protection against radiation: chelating agents (119), carbon monoxide (120, 121), chlorpromazine (122), 4-acylpyrogallol (123), atabrine (124), agents concerned with the peroxide-catalase hypothesis (125) and cyanide (39). Protection with carbon monoxide administered after irradiation has been reported (121). The possible mechanisms of action of some of these compounds has been discussed by Alexander (21). Tenchov *et al.* (126) reported protection in rats with strychnine given *after* irradiation. The drug was of no value if given prior to exposure.

Oxygen effect, hypoxia, hypothermia.—Stender & Hornykiewytsch (127, 128) in an extensive series of experiments confirmed the fact that protection is afforded rats if irradiation is carried out at oxygen tensions below 10 per cent. Protection was demonstrated in normal and adrenalectomized animals, as well as in animals pretreated with cortisone and thyroxine. Chlorpromazine markedly enhanced the protection afforded by hypoxia when given prior to irradiation. Rambach *et al.* (129) compared bone marrow cellularity and DNA synthesis following irradiation in the normal and hypoxic state. At 96 hours after irradiation, the hypoxic animal had slightly more cellu-

larity and marked increase in DNA synthesis over the control animals. The hypoxia reduced the effect of 800 r on bone marrow to about that seen after 600 r. The effects of irradiation under hypoxic conditions on various tissues was described (29 to 43).

Conger (130) found the sensitivity of ascites tumor cells irradiated under increasing oxygen tensions to increase to a plateau. The results may indicate a practical application in clinical radiotherapy. An increase in the relative biological effectiveness of neutrons on ascites tumor cells irradiated in oxygen, over that for cells irradiated in nitrogen was also observed. Howard-Flanders and Wright (131, 132), using the rate of growth of the mouse tail as the end-point, demonstrated increased sensitivity to x-rays and fast neutrons with increasing oxygen tension.

O'Brien, Frank & Garner (133) reported lessened cutaneous effects of radiation on ischemic rabbits' ears cooled to 10° C. during irradiation. Allen (134) showed that hypothermia reduced the sensitivity, and fever increased the sensitivity of rats to WBR. Hajdukovic (135) irradiated rats at 14 to 15° C., and found enchanced survival, to the same degree, if irradiation was carried out in oxygen, or under air pressure of 1.25 atmospheres. The results indicate that hypoxia may have little to do with protection by means of hypothermy. Hornsby (136), by chilling mice to 0 to 1 degrees centigrade has obtained 100 per cent 30-day survival (36 mice) at x-ray doses of 900 r to 1500 (higher dose not attempted). The LD_{50} for the strain used is 620 r. The proportion of protection afforded by hypothermia, and by the severe degree of resulting hypoxia, cannot be ascertained.

Combined procedures.— In earlier studies, Cole & Ellis (137) had shown an additivity in protection against x-rays by cysteine plus sodium nitrite at dose levels of WBR, where neither agent alone would afford protection, and they deduced that the agents protected through different mechanisms. Devik (30) has studied the combined protective effect of cysteine and hypoxia on mortality and chromosome aberrations of bone marrow in mice. Cysteine and hypoxia yielded more protective effect when administered together rather than separately. Gros & Comsa (138) claim protective effects of combined cysteamine and thymus extract. With a combination of an SH compound before exposure, and bone marrow and streptomycin after exposure, Burnett & Doherty (139) were able to triple the LD_{50} for mice. Lothe & Devik (140) found that cysteamine seemed to confer some additional protection to rabbits' ears irradiated in the hypoxic state, interpreted by the authors to indicate that the two protective methods act to some degree along different paths.

Bond & Carter (141) have shown that a combination of cysteine and nitrite will afford some protection to mice against fast neutrons. Marked protection would not be anticipated, since, in theory, competition for free radicals should become less important as the LET increases, as it does with alpha particles. Patt *et al.* (36) reported that cysteine had relatively little protective effect against fast neutrons.

Late effects genetic effects.—Hollaender & Kimball (142) have discussed the possible modification of radiation-induced genetic damage, and state that genetic damage can be protected against by pre-treatment, not as yet by post-treatment. Devik & Lothe (143) gave cysteamine or cystamine prior to 200 r WBR and reported protection against radiation-induced chromosome aberrations in the 110 mice studied. Riley (144), using onion root tips, found sodium hydrosulfite and 2, 3 dimercaptopropanol to be effective against x-ray induced chromosome interchanges and deletions, but not against aberration frequencies of the mitotic process detectable by cytological observation. The chemicals themselves produced no consistently demonstrable effect on the mitotic process. Kaplan and Lyon (53) have reported failure of pre-protection against genetic damage.

Brecher *et al.* (145) and Finnerty *et al.* (146) showed that rats protected against 30-day mortality by means of parabiosis, glutathione, or PAPP, later developed a variety of malignancies. Similar results have been reported by Maisin (48) in animals receiving MEA. Bennett *et al.* (147) found that rats protected against early lethality by hypoxia, later showed shortening of life span, generalized arteriosclerosis, hypertension, cataracts, and cachexia. It appears definite that pre-protection is efficacious against early, but not late, effects of radiation.

Intensifying agents.—The studies on intensification of x-ray effects initiated in 1946 by Mitchell are continuing (148, 149, 150). It appears that synkavit and other related compounds of the Vitamin K group will increase the mortality of irradiated animals. The material tends to concentrate in some tumors following intravenous injection. Clinical trials on human cancer of the lung are encouraging. It is conceivable that substances that intensify the effect of ionizing radiation could be coupled with B_{10} and irradiated with slow neutrons after administration, thus, possibly availing one of the B_{10} (n, α) Li^7 reaction and the enhancement resulting from chemical intensifiers of radiation. Irradiation effects have also been increased by oxygen poisoning in mammals (151, 152).

Increased Survival Rate by Biological Means

The pattern of degenerative histopathologic changes in radiation injury has been known for decades. It is not necessary to review the spontaneous degenerative course here, for the subject matter is covered elsewhere (1, 3, 6, 8, 9 to 12). Spontaneous regeneration has not been studied as extensively. The degree of radiation injury is dose-dependent over certain ranges. Threshold doses for observable effect and doses for maximum effect limit the usefulness of biologic systems for radiation dosimetry to narrow ranges that vary with the system. The use of quantitative measurements on mammalian systems for the estimation of the degree of degeneration and restoration of irradiated tissues with appropriate references has been considered (12, 13). After doses of radiation from which there is survival, spontaneous regeneration of most tissues occurs. However, it is possible to have permanent

atrophy of some tissues that are not essential to life, or of portions of tissues that are essential to life.

In addition to any factors that favorably influence the survival rate following irradiation the authors are particularly concerned with trying to interpret the mechanism of action of procedures that accelerate the spontaneous regeneration of irradiated tissues. Restoration has been adopted as the most appropriate term in this connection, following Latarjet & Gray (14). Earlier work on induced restoration has been reviewed (2, 3, 5 7 to 11, 153 to 156). It is well established that restoration of the hemopoietic phase of radiation injury can be accelerated, that the course of the radiation syndrome can be altered, and that the 30-day survival rate can be markedly improved (2, 3, 7 to 11, 153 to 155). It is not clear what influence the restoration has on ultimate longevity, genetic effects and tumor induction [see section on cancerogenesis in last year's review, (1)]. However, Maisin *et al.* presents data (156) suggesting that protective measures do not alter radiation-induced tumor induction. These observations are consistent with parabiotic studies of Brecher *et al.* and Finerty covered in last year's review. Early studies on shielding and restoration of irradiated tissues go back to Chiari (1912) and Fabricius-Möller (1921) (c.f. 153). During the development of atomic weapons (1943 to 1946), Jacobson and associates made considerable progress in the problem of accelerating regeneration of hemopoietic tissues. Their studies led to the concept that "humoral factors" were present in the shielded spleen of the irradiated mouse which induced rapid restoration of the irradiated hemopoietic tissues elsewhere in the body. Their work and concepts are summarized in reviews by Jacobson *et al.* (154, 155). As a result, investigations on proof of the existence and isolation of the "humoral factor" have been conducted by workers in a number of laboratories.

Hilfinger *et al.* (157) reported increased survival rate of irradiated rabbits when homologous bone marrow was injected intravenously three days after irradiation. The peripheral blood counts of control and treated animals were similar. Sterile inflammation induced by turpentine injections after irradiation altered the neutrophil-leukocyte count and was followed by an increased survival rate when dogs were exposed to mid-lethal doses of radiation [Schlang *et al.* c.f. (158)]. When irradiation doses were raised to supralethal levels, however, no protection was afforded. Lorenz & Congdon (159, 160) have reported that homologous and heterologous ground bone favorably modify lethal radiation injury in the mouse. Transplanted homologous bone developed bone marrow, but heterologous bone transplants did not show bone marrow formation. The same investigators reported protection of some strains of mice by intravenous injections of rat bone marrow emulsion from certain strains of rats. They interpreted the bone and bone marrow transplant studies as evidence in favor of the existence of a humoral factor. Cole *et al.* (161) protected mice with rat bone marrow. Late deaths after two weeks were common. Hirsch *et al.* (162) compared the effect of isologous, homologous, and heterologous bone marrow in irradiated mice. Their test

object is the mouse which had been submitted to four single weekly irradiations to produce marked thymic atrophy. After the last irradiation 10^6 bone marrow cells suspended in Tyrodes were injected intravenously and thymic regeneration was followed. By the use of cross responses in F_1 hybrids they demonstrated that the recovery factor is highly strain specific—only isologous marrow being effective, and homologous and heterologous marrow being ineffective. It is not clear why this response is genetically specific and why other responses are in part modified by heterologous factors.

In unconfirmed experiments, Ellinger (163) reported beneficial effects on the survival rate in irradiated mice following injection of cell-free aqueous extracts of normal spleens. Goldwasser & White (164) claim that noncellular extracts of hog intestinal mucosa confer some protection to irradiated mice.

In other experiments Smith *et al.* (165) have shown that the injection of particulate matter (quartz, glass, and limestone) 44 to 74 microns in size and 5 to 50 mg. intraperitoneally after irradiation increased the survival rate of mice. In view of the relation of time of injection to effect the authors related the protective effects to an enhancement of the animals' defenses against infection through an undisclosed mechanism. Jacobson *et al.* (166) have increased the survival rate of irradiated rabbits by the post-radiation injection of mouse embryo cells or baby mouse liver or spleen cells without any effect on the hematologic recovery in the peripheral blood. Marrow studies are not yet reported. Bohr, *et al.* (167) studied the the effect of renal shielding on radiation induced vascular hypersensitivity. They found that the animals in whom the kidneys were shielded, while the rest of the body received 650 r, appeared healthier and did not develop the increased vascular sensitivity. They felt the increased vascular sensitivity paralleled the debility and did not reflect the presence of a renal vasoexcitor material since irradiation of kidneys alone did not produce the response. As a result of these studies the authors studied the effect of renal shielding on survival rate (168) and found in an as yet unconfirmed experiment that the survival rate was markedly enhanced. Jacobson *et al.* (169) in earlier studies with mice and renal shielding found no protection. The studies of Hilfinger *et al.* (157), Smith *et al.* (165), Jacobson *et al.* (166), and Bohr *et al.* (167, 168) strongly suggest that survival from radiation injury in the mid-lethal range may be enhanced without accelerating restoration of hemopoietic tissues, nor shielding or using known hemopoietic tissues. However, in respect to the kidney studies, that organ is the site of hemopoiesis in lower forms and is occasionally the site of extramedullary hematopoiesis in man, a subject considered by Saleeby in 1903 (170).

Allen *et al.* (171) have injected cell free plasma collected from the splenic vein of normal rabbits into irradiated rabbits and detected a small protective effect. Mortality of 96 per cent was reduced to 76 per cent. The authors consider this proof of existence of a non-cellular protective factor that can be elaborated by the spleen. Further studies to confirm these results and determine whether the factor has the same chemical properties (lability, etc.)

as the hypothetical factor that Cole and associates (172 to 180) have pinpointed to the nucleus fraction of splenic homogenates are needed. Congdon *et al.* (181) have given transfusions of separated leukocytes obtained from mice who had an extreme leukocytosis[3]. The protective effect was correlated with the granulocyte count of the transfused cells. It is probable that immature cells would also be present in the transfused cells thus complicating the interpretation of whether the mature granulocytes transported the protective factor or whether totipotential immature cells were seeded.

Cole and associates (172 to 180) have been most productive in investigating the possible existence, and subcellular location of the protective "spleen factor." Early in their work it became evident that age, strain, and species were factors that influenced the results (172). Approximately four times as much spleen on a weight basis was required to give equal protection when spleens from adult donor mice, as compared to one week old donor mice, were used. A converse age effect was observed with recipients. Significant protection was obtained with 10 to 11 week old recipient mice, and no protection with five week old mice. Following their earlier work on accelerated restoration of hemopoietic tissues by post-radiation injection of splenic homogenates, Cole *et al.* (173) tested the effectiveness of several subcellular fractions of spleen homogenates prepared by the Schneider-Hogeboom techniques. The experiments conclusively showed that there was no restorative effect connected with the mitochondria, microsomes or soluble supernatant fractions. The restorative effect was found only with the cell nucleus fraction. Since relatively few intact cells were found on stained smears of the nucleus fraction, it was believed that their experiments strongly supported the concept that the restorative effect was noncellular and associated with the nucleoproteins. Further studies on the splenic homogenates (174, 175) have shown that DNAase and trypsin inactivate the material, as does distilled water extraction under various conditions. Since enzymes are believed not to attack living intact cells, these experiments are interpreted as indicating that the active principle is associated with DNA and not necessarily with living cells. These contensions argue strongly for the noncellular concept. However, it is believed that more stringent restrictions are necessary for proof, as will be discussed later at the conclusion of the review of current research. Since earlier work had shown that splenic shielding and splenic homogenates gave little protection to rats, and, since spleens that manifest marked protective effect normally contain extensive myelopoiesis, intravenous bone marrow injections were tried with protection in rats (180). The effect was relatively minor, however, which may be due to the predominance of "intestinal deaths" in rats, a syndrome that is not modified by bone marrow injection. Swift, Taketa, & Bond (182) studied the protective effect of injections of bone marrow and of shielding of the spleen or leg in irradiated rats whose intestines were shielded and compared results to protective studies in the mouse. The results suggest that there is a synergism of protective effect between the bone marrow and the small intestine, a conclusion that was also arrived at by Maisin *et al.* (183).

In continuation studies on the mouse splenic homogenates, Cole *et al.* (177) have shown that DNAase has little activity on liberating DNA from spleen cells prepared by floating the cells out into glucose saline solution and marked liberating action when homogenates are prepared by a glass homogenizer. These experiments strongly suggest that homogenization seriously injures the surface of the cells so that the cells are subject to attack by the enzymes used. In addition, the subcellular fractionation studies were extended to rat bone marrow and found to apply. Marrow removed from rats two days after 725 r WBR had no activity. It was also shown that the active factor was non-dialyzable, unstable, heat-labile and radio-sensitive *in vitro* (178). The activity was not increased by erythroid hyperplasia of the spleen and no activity was found in homogenates of muscle, lung, thymus or liver. Since the activity apparently was associated with DNA of myeloid elements (not lymphoid or erythroid) the authors suggested "that the mechanism of action of the spleen (and bone marrow) factor(s) may possibly be related to a self-duplication or autocatalytic phenomenon, leading to the new formation of specific desoxyribonucleo-protein required for mematopoiesis." In addition, these workers have demonstrated that the DNA level of the spleen can be used as a sensitive early index of recovery from radiation injury of hemopoietic tissue, and suggested that this index may be a quick, effective method of assaying for presence and activity of the active restorative factors. The same group has studied incorporation of C^{14} formate into nucleic acid purines from control irradiated, and spleen-homogenate-treated, irradiated mice (179). The inhibition was detectable by five hours after irradiation, and negligible incorporation was present from the second day until death in untreated animals. In the spleen-homogenate-treated animals, DNA-adenine began to return by the fifth day after incorporation of C^{14} formate into spleen and bone marrow. Snythesis into guanine lagged. Ungar *et al.* (184), in a single experiment, report that spleen homogenates protect against beta-ray effects on the rat skin. Because of the difficulty of adequately quantifying the degree of radiation damage to skin, their study requires confirmation. To these reviewers it is difficult to conceive of splenic protection of skin.

Parabiosis induced after irradiation has been shown to increase the survival rate of irradiated rats. The nature of this effect has been pursued by Finerty and associates (185 to 188). It was shown that parabiosis of a splenectomized, adrenalectomized, or hypophysectomized rat to the irradiated rat resulted in an increase in survival rate similar to that obtained with normal rats, and it was concluded that the effect was not mediated through spleen, adrenals, or hypophysis (185, 186). The influence of time and duration of parabiosis on survival of the irradiated rat was also investigated (187). Parabiosis, if instituted on the fourth post-irradiation day, still conferred some protection. Since it takes 2 to 3 days for effective union and since animals begin to die around the eighth day, these authors concluded that the critical period in the rat lies between the sixth and tenth days. This is the time during which granulocytes and platelets are at, or are

approaching, minimal levels. The peripheral blood was also studied during parabiosis of normal with irradiated rats (188). The nonirradiated parabiont developed a neutrophilic leukocytosis. There was an earlier regeneration of peripheral blood counts in the irradiated parabionts, commencing about the fourth post-irradiation day, with return to normal by the eighth to tenth day. This alteration could be due to transfer of cells. However, since earlier work (c.f. 2, 3, 153 to 155) showed that marrow regeneration occurred sooner, the peripheral blood changes in parabiosis of an irradiated to a normal rat was probably a combination of both accelerated restoration and continuous transfusion of formed elements. In fact, Binhammer *et al.* (189) have also shown that an early regeneration of the hemopoietic tissues is characteristic of parabiotic protection. Genaud & Meot (190) found that the combined action of streptomycin and hematopoietin increased the survival rate of mice given otherwise lethal doses of radiation. May & Arpiarian (191) transplanted marrow from infant mice to adult irradiated mice and obtained protection.

Maisin *et al.* (48, 156, 183, 192 to 200) of the University of Louvain, Belgium, have been most prolific in the study of combined effects of shielding various organs, of injecting mercaptoethylamine before exposure and injecting marrow or spleen after exposure. Their work is summarized in English (156). Early in their studies on the inter-relations of spleen, bone marrow and liver to hemopoietic regeneration following irradiation they concluded that liver shielding was critical. However, external shields of the liver also protect portions of the bowel and bone marrow, factors which, by themselves, will protect significantly against radiation injury. Apparently, this group has reversed its position on the role of the liver (198). They also showed the basic importance of shielding bone marrow by comparing shielding of paws in which bone had been removed to intact shielded paws (198), a conclusion which is consistent with the results of workers throughout the world arrived at independently by other approaches. When exteriorization of organs was resorted to in independent studies they arrived at the same conclusions on the importance of bone marrow and gastrointestinal tract and the relation of these structures to specific radiation syndromes as described earlier in this country (see Ref. 182, 201, 202, 203) for summary and earlier references]. They have described a synergistic protection of shielding bone marrow and intestine simultaneously.

Shielding studies of various types continued. Lamerton *et al.* (204 to 207) have compared the effects of WBR, partial body irradiation (upper or lower half), administration of Au^{198}, of P^{32} and WBR with pre-treatment with cysteinamine. In general, a correlation was found between the severity of the acute phase (commencing approximately 10 days after irradiation), and the degree of anemia. Partial body irradiation lessened the severity of the acute phase. The clinical radiation syndrome of the rat was systematically described by these workers. In continuation of studies on the radiation-induced anemia, Lamerton *et al.* (206) have explored the in-

fluence of shielding and relationship to platelet changes. Shielding of head or leg, but not of a loop of skin reduced the anemia and thrombopenia. It appeared that the severe anemia developed after platelet levels fell below 30,000 per cubic mm. In shielded animals, platelets remained above 40,000 per cubic mm. Baxter *et al.* (207) have summarized their experience on irradiated rats and presented data illustrating the usefulness of Fe^{59} in quantitative studies of erythropoiesis to elucidate the influence of shielding and other protective measures against radiation injury. They point out the value of fecal Fe^{59} excretion to follow quantitatively gastrointestinal hemorrhage. Keriakes *et al.* (208) exposed rats to equal volume doses of x-radiation through lead grids with holes of varying size, designed so that the ratio of open to shut areas remained constant. The smaller the holes, the greater the survival rate. They postulated that the effect may be explained by a beneficial effect of adjacent normal tissue on recovery of the irradiated tissue, since survival appeared related to the area of interface between normal and radiated tissue.

Swift *et al.* (209) have successively irradiated portions of the body, followed after varying time intervals with irradiation of the entire remaining portion of the body. This procedure significantly increased the survival rate. Of particular interest was the fact that the spleen could be irradiated with 900 to 1000 r, with subsequent shielding with lead, while the rest of the body was given a similar dose, and still the survival rate was increased. These studies prove quite conclusively that the protective factor circulates and can be quickly picked up by tissues that have been irradiated. Swift & Taketa (203) have studied the influence of shielding a portion of the small bowel on the recovery of intestinal weight. The weight recovery was hastened but without discernible acceleration in histologic recovery, hence the probability of a "specific intestinal restorative factor" is unlikely but not disproved. Brown *et al.* (210) have studied the biologic aspects of the marrow anti-radiation factor, using restoration of thymic weight as the index of effectiveness. The active factor from marrow was unable to penetrate through a porous implanted intraperitoneal capsule. The active principle was found associated with the cell nucleus fraction, thus confirming in part the conclusions of Cole *et al.* (173). Induction of erythroid or myeloid hyperplasia of the spleen did not increase restorative activity. This implies that the active factor resides in more primitive cells than those morphologically connected with obvious erythropoiesis and myelopoiesis, and that spleens without normal myeloid metaplasia would have no restorative effect. The radioactivity from homologous marrow labelled *in vitro* with P^{32} was found in the reticuloendothelial system, but most of the activity was not accounted for. Freezing and lyophilization destroyed the activity. Duplan (211) has studied protection by embryonic liver of mice. His studies prove the implication stated above that the active factor whether it be biochemical or cellular is associated with hemopoietic elements that are morphologically undifferentiated.

The British group (Barnes & Loutit) have made a series of contributions (212 to 216) on the nature of the restorative action of splenic implants and homogenates. Initially, they confirmed the effectiveness of splenic homogenates. Next, they showed that immunization of one strain of mouse (CBA) by strain A material prevents protection; whereas, short-lived protection of CBA mice could be obtained by use of strain A material in nonimmune mice (258). Further, they were unable to confirm the heterologous protection experiments of Lorenz *et al.* (217). In general, their experience was the same as Cole *et al.* (173) in that freezing, thawing, irradiation, and formalin-treatment inactivated the principle. Their more recent studies (215) showed that the restorative principle of infant CBA mice spleens can be preserved when the spleens are equilibrated with glycerol serum and stored at −70° C. for as long as 83 days.

Booz (218) and Betz, Booz, & Firket (219), in definitive experiments, irradiated mouse spleens *in vivo* and *in vitro*, and immediately implanted the organs subcutaneously in normal hosts. They found 1000 r (well above the LD_{50} for the animals) did not detectably affect the hemopoietic regeneration capacity of the organs, and 5000 r only slightly delayed regeneration. Forty thousand r was required for complete failure of regeneration. From this they conclude that the inhibition of hemopoiesis in total body radiation cannot be explained by direct tissue lesions alone, but that general metabolic disturbances within the body must play a significant role.

Another type of modification of radiation injury by biological means has been reported by Stohlman *et al.* (220). It was found that anoxia produced by PAPP-induced methemoglobinemia, or bleeding before or after irradiation, modified the response of erythropoiesis by inducing an early reticulocytosis and more rapid recovery of hemoglobin levels when exposure was in the sublethal range. In addition (221), the injection of plasma from anemic animals into sublethally irradiated rats increased the Fe_{59} incorporation into red cells. From these studies, it was concluded that erythropoietic tissue could respond to a physiologic stimulus following irradiation, providing the injury was not too severe. Savitsky (222) has reported in unconfirmed experiments that a crude protein extract of beef spleen may favorably affect post-irradiation hemorrhage in dogs.

In general, one can divide post-radiation modification of hemopoietic injury into three general categories: (*a*) the striking and rapid restoration of severely damaged, hemopoietic tissues by shielding of bone marrow or spleen, parabiosis, bone marrow, or splenic homogenate injection, etc., which are effective following usually lethal doses of irradiation from which spontaneous recovery is rare; (*b*), the less striking effect of post-radiation stimulation of myelopoiesis and erythropoiesis. The former can be induced by sterile inflammation [c.f. (153)] in the mid-lethal or sublethal, but not in the absolute lethal zone. Erythropoiesis is stimulated by anoxic stimuli or by normal anemic plasma in the sublethal range only; (*c*) modification of the histologic and clinical picture by substitution (see earlier reviews) (red

cell, white cell, and platelet transfusion) without greatly increased survival rate or induced restoration of hemopoietic tissues. The last category simply represents substitution of elements that are no longer being produced. In the second category one can imagine the mechanism as being due to the stimulation of precursor cells that are injured, but still capable of responding to physiologic stimuli (erythropoietin, leukocytosis promoting factor, etc.) that are known to exist, although not yet adequately characterized. Interest has centered mainly around the mechanism of the restorative effect in the first category. The following alternatives are feasible:

(*a*) Direct transplantation or seeding of precursor cells from the shielded organ or injected material into the recipients' hemopoietic tissues, with all new growth coming from the donor cells.

(*b*) Transplantation, producing temporary growth of new cells, thus tiding the recipient over the critical period until its own hemopoietic tissues recover.

(*c*) Provision of cells or highly organized material which produces a factor that accelerates regeneration of the recipients' precursors of all formed elements.

(*d*) Provision of a humoral, non-cellular factor that stimulates the regrowth of all parts of the recipients' injured hemopoietic tissue.

Obviously, all of the groups working on the restoration of irradiated hemopoietic tissues are aware of these alternative possibilities; however, despite the intensive efforts of diverse groups, the problems have not been resolved satisfactorily. Certain facts do stand out. First, the materials that can be injected or organs that can be shielded and give significant protection after normally lethal doses contain the necessary precursor cells. The spleens of most strains of mice contain precursors of red cells, granulocytes, platelets, and lymphocytes. In strains of animals where "normal myeloid metaplasia" is absent or sparse in the spleen, one obtains no restoration or decrease in mortality. Thus, the term "*splenic factor*" is misleading. The "restorative factors" are associated with, or, at least concentrated in, myeloid tissue, since lymphoid transplants (223) and transfusion of lymphocytes [Campbell, c.f. (153)] are ineffective. Certainly, when the proper intact, genetically acceptable cells are shielded or introduced, one gets good restoration after doses of radiation that uniformly produce 100 per cent mortality. The subcellular fractionation studies of Cole *et al.* (173) confirmed by Brown *et al.* (210) conclusively prove that the "restorative effect" is not carried along with the microsomes, mitochondrial, or soluble supernatant fraction. The "restorative effect" resides with the cell nucleus fraction. It is destroyed by freezing and thawing, gentle extraction, irradiation, room temperature or 5° C. storage, and by DNAase and trypsin. The latter studies imply that homogenates and cell nucleus fraction consist predominantly of injured cells, since enzymes do not attack intact viable cells. Since Goldwasser & White (164) have shown that some DNAase preparations are contaminated with other enzymes the exact interpretation of these studies

is confused to say the least. Furthermore it has not been proved that all cell types in the homogenates are dead and not capable of undergoing repair and subsequent division upon injection into a compatible donor. Admittedly, these studies strongly support the concept of restoration by a nonviable cellular component, the cell nucleus, and appear to pinpoint the activity to the nuclear DNA fraction. However, it is most difficult, if not impossible, to distinguish the bare nucleus of many hemopoietic cells from cells which normally possess but a slight shred of cytoplasm when unstained wet preparations are studied by dark phase contrast microscopy. A method has been devised by Brown (224) for determining viable cells in homogenates and nuclear fractions of cells. In fact, he has demonstrated quite convincingly that whole cells are present in large numbers in the nuclear fraction of thymus homogenates. Repetition on homogenates of spleen and bone marrow would help in large part to resolve the difficulties in interpreting studies on the nature of spleen and marrow protection. Cole's studies do prove that the manipulations have injured the cells, but do not prove the critical point, and that is whether these injured cells, many devoid of most of their cytoplasm, are able to undergo repair, mitosis, and maturation when injected into the proper host. Perhaps tissue culture techniques may, in part, answer these problems. In fact Miller (225) has shown that tissue cultures of spleen or embryo liver will protect mice provided that the culture is grown in rabbit serum but not if grown in synthetic media or in heat inactivated serum. Extension of these studies might answer the above questions. Certainly this implies that there are chemical factors upon which the protective cells are dependent. Whether these culture factors are radioresistant or present in the fatally irradiated animal will be of considerable interest. Barnes & Loutit's (214) studies on controlled freezing and thawing in which morphologic integrity of the splenic cells were preserved, along with the full efficacy of the "restorative effect," strongly implies that intact morphologic entities are essential. Jacobson's earlier observations on the rapidity with which erythropoiesis extends through the shielded spleen after irradiation of the rest of the animal or when Sr^{89}, a bone seeker, is administered, strongly suggests that at least the erythropoietic humoral factors persist in the irradiated animal, and that nonirradiated erythropoietic centers normally in the spleen are able to respond to a surplus of erythropoietic factors. It has been reasoned that a heterozygous source of the restorative factor would prove that the effect was humoral in origin. However, the studies of Barnes & Loutit (214) that heterozygous transplants are effective only temporarily in irradiated animals which are known to be poor antibody producers and in which previous immunization prevents any restorative effect, seems to put this concept to rest. The studies prove that for lasting restoration the factor must be antigenically acceptable, be it cellular or chemical. The parabiotic studies (187, 188) and the most recent studies of Brown *et al.* (210) and shielding studies of Swift *et al.* (209) indicate that the factor circulates, is not permeable to a porous membrane and,

apparently, is associated with a cellular entity that is more primitive than the actively dividing cells present when erythroid and myeloid metaplasia has been induced experimentally [Brown *et al.* (210) and Duplan (211)].

Recently very significant studies, incontrovertible when considered together, have been reported independently by three different laboratories[4] conclusively proving that cellular transplanatation can and does take place. Lindsley *et al.* (226) availed themselves of the blood type of certain strains of rats and proved that functional erythropoietic tissue of the donor animal was implanted in the irradiated host and was producing cells characteristic of the donor. As pointed out by Ford *et al.* (227) this might be comparable to transduction in bacteria. Nowell *et al.* (228) took advantage of the fact that rat leukocytes give a strong positive alkaline phosphatase and mouse leukocytes give a negative reaction. Irradiated mice were injected with rat bone marrow. This increased the survival rate. Phosphatase positive white blood cells were found in the peripheral blood and the bone marrow showing that transplantation had in all probability occurred. However, these authors do not rule out that the phenomenon may have been induced in the host cells, a rather unlikely explanation. Ford *et al.* (227) have without doubt, proved that transplantation of donor hemopoietic cells has occurred. They used a distinctive "marker chromosome" that had been induced by a radiation reciprocal translocation of chromosomes yielding a small distinctive easily detected chromosome. When spleen homogenates were prepared from the spleens of mice possessing this distinctive chromosome, the proliferative hemopoietic tissue of recipient mice consisted predominantly of the marked cells. Makinodan (229) by quantitative immunologic tests on red cells proved that irradiated mice heterologously protected by rat bone marrow eventually developed 100 per cent rat red cells and also confirmed Nowell *et al.* (228) on the presence of rat granulocytes by the distinctive phosphatase reaction. It would appear that these four studies would have driven the last "coffin nail" into the "humoral theory of Jacobson"; however, proof of transplantation does not exclude a humoral contribution. In fact, Jaroslow & Taliaferro (230) have apparently demonstrated that there is a noncellular factor associated with diverse materials such as spleen mince, HeLa cells, and yeast autolysate that restores the ability to produce antibodies. Miller (225) has also demonstrated a heat labile serum factor that is necessary to retain the protective effect of cells of embryo spleen or liver in tissue cultures, although the factor is not necessary for viability of the culture.

In general then, one must accept that cellular transplantation is a proved fact. The evidence indicates that the protective cell is intermediate between the primitive mesenchymal cell and the actively proliferating differentiated cell since tissues rich in primitive mesenchymal cells do not pro-

[4] Oak Ridge National Laboratory, U. S. Naval Radiological Defense Laboratory, and Atomic Energy Research Establishment, Harwell, England

tect. If this concept is true, one would postulate that factors concerned with active division and maturation for any lineage are abundant in the irradiated animal, but that the cells which can respond to the stimuli have been eradicated. There is good histologic evidence for this. The defect then might be an inability of the primitive mesenchymal cells to mature to the stage where they can respond to stimuli that are present. Answers to certain speculative propositions are vital to an understanding of the mechanism of induced restoration:

(*a*) Can a cell nucleus of a totipotential hemopoietic cell from which the cytoplasm has been largely ground off, undergo repair and migrate to hemopoietic sites and re-establish all lineages of blood cells?

(*b*) Does the cell nucleus fraction of splenic or bone marrow homogenates contain totipotential cells that have so little cytoplasm that one cannot recognize these entities?

(*c*) What happens to the injected homogenates or cell nucleus fraction? i. Are they phagocytosed, and where? ii. If phagocytosed, is a substance released in close proximity to the recipient's potential precursor cells that induces and accelerates hemopoiesis? iii. Do the injected cells settle down in the tissue of origin and reproduce? iv. If established in the tissue of origin in the recipient, do they then influence the recipient's irradiated cells to divide and differentiate? v. If a substance is released or produced by the donor's cells or cell nuclei, does it circulate, or must it be almost a cell-to-cell transfer?[5] Ultimately, the problem comes back to answering the more general old hemopoietic problem on the *de novo* origin of myeloid metaplasia. Is it autocthonous or metastatic? If autocthonous, is it induced by circulating chemical factors? From all the experimental evidence today it is proved that cell transplantation does occur but one cannot exclude humoral contributions of the recipient and possibly of donor material. The restorative effect is genetically specific and is associated with primitive myeloid cells. In conclusion, it appears probable that the basic defect in fatally irradiated animals is an absence of cells of sufficient maturity to respond to physiologic factors of growth and differentiation that are present or can be released by appropriate stimuli in the irradiated animal. The restorative effect can be produced by introduction of cells in the depleted area with this degree of maturity, or presumably by a chemical influence that initiates heteroplastic hemopoiesis. The cellular explanation is a reality with shielded spleens or bone marrow, and with injected myeloid suspensions. A chemical influence is still an attractive hypothesis, the relative importance of which in repairing radiated tissues remains obscure.

[5] This review was originally written in 1955 and not published *in toto* because of space limitations. When it was brought up to date in July, 1956, it appeared that the answer to "c" above may be "yes," to "d," no and to "e," no substance is released (226 to 229). Since it appears useful in considering the growth of knowledge and design of experiments the hypotheses of 1955 are left in the text although apparently answered in 1956.

LITERATURE CITED

1. Cronkite, E. P., and Bond, V. P., *Ann. Rev. Physiol.*, **18**, 483–526 (1956)
2. Patt, H. M., *Ann. Rev. Physiol.*, **16**, 51–80 (1954)
3. Bacq, Z. M., and Alexander, P., *Fundamentals of Radiobiology* 00–00 (Butterworth Scientific Publications, London, England, 389 pp., 1955)
4. Lea, D. E., *Actions of Radiation on Living Cells* (Cambridge University Press, Cambridge, England, 416 pp., 1955)
5. Howard, A., and Ebert, M., *Nucleonics*, **11**, 18 (1953); *Acta Radiologica, Suppl.* 116, (1954)
6. *Proc. Radiobiol. Sympsoium, Liége* Bacq, Z. M., and Alexander, P., Eds., Butterworth Scientific Publications, London, England, 362 pp., 1955)
7. Ord, M. G., and Stocken, L. A., *Physiol. Revs.*, **33**, 356–86 (1953)
8. Patt, H. M., *Physiol. Revs.*, **33**, 35–76 (1953)
9. Hollaender, A., Ed., *Radiation Biology*, **1**, Part 1 and 2 (McGraw-Hill Book Co., Inc., New York, N. Y., 1269 pp., 1954)
10. Sparrow, A. H., and Forro, F., Jr., *Ann. Rev. Nuclear Sci.*, **3**, 339–68 (1953)
11. Furth, J., and Upton, A. C., *Ann. Rev. Nuclear Sci.*, **3**, 303–38 (1953)
12. Cronkite, E. P., Brecher, G., Conard, R. A., and Chapman, W. H., *Glutathione Symposium* (Academic Press, Inc., New York, N. Y., 1954)
13. Storer, J. B., and Langham, .W H., *Radiation Research* (In press)
14. Latarjet, R., and Gray, L. H., *Acta Radiol.*, **41**, 61–62 (1954)
15. Bacq, Z. M., *Acta Radiol.*, **41**, 59–60 (1954)
16. Bacq, Z. M., and Herve, A., *Strahlentherapie*, **95**, 215–37 (1954)
17. *Proc. Intern. Conf. Peaceful Uses Atomic Energy* (United Nations, New York, N. Y., 402 pp., 1956)
18. *Progress in Radiobiology* (Mitchell, J. S., Holmes, B. E., and Smith, C. L., Eds., Oliver and Boyd, London, England, 557 pp., 1956)
19. Butler, J. A. V., *Radiation Research*, **4**, 20–32 (1956)
20. Alexander, P., *Brit. J. Radiol.*, **26**, 413–16 (1953)
21. Alexander, P., Bacq, Z. M., Cousons, S. F., Fox, M., Herve, A., and Lazar, J., *Radiation Research*, **2**, 392–415 (1955)
22. Alexander, P., and Fox, M., *J. chim. phys.*, **50**, 415–22 (1953)
23. Doherty, D. G., and Burnett, W. T., *Proc. Soc. Exptl. Biol. Med.*, **89**, 312–14 (1955)
24. Gray, S. L., Moulden, E. J., Tew, J. T., and Jansen, H., *Proc. Soc. Exptl. Biol. Med.*, **79**, 384 (1953)
25. Salerno, P. R., and Friedell, H. L., *Federation Proc.*, **12**, 364 (1953)
26. Salerno, P. R., Uyeki, E., and Friedell, H. L., *NYO Report*, 4924 (1955).
27. van Bekkum, D. W., and Cohen, J. A., Proc. Intern. Conf. Peaceful uses of Atomic Energy, pp. 330–331 (United Nations New York, N. Y., 1956)
28. van Bekkum, D. W., and de Groot, J., *Progress in Radiobiology*, pp. 243–248 (Mitchell, J. S., Holmes, B. E., and Smith, C. L., Eds., Oliver and Boyd, London, England, 1956)
29. Gray, L. H., *Progress in Radiology*, pp. 267–278, (Mitchell, J. S., Holmes, B. E., and Smith, C. L., Eds., Oliver & Boyd, London, England, 1956)
30. Shapiro, B., and Eldjarn, L., *Radiation Research*, **3**, 255–66 (1955)
31. Shapiro, B., and Eldjarn, L., *Radiation Research*, **3**, 393–99 (1955)
32. Eldjarn, L., Pihl, A., and Shapiro, B., *Proc. Intern. Conf. Peaceful Uses Atomic energy*, pp. 335–341 (United Nations, New York, N. Y., 1956)

33. Eldjarn, L., and Pihl, A., *Progress in Radiology*, pp. 249–259, (Mitchell, J. S., Holmes, B. E., and Smith, C. L., Eds., Oliver & Boyd, London, England, 557 pp., 1956)
34. Langendorf, H., Koch, R., and Hagen, U., *Strahlentherapie*, **97**, 218–30 (1955)
35. Devik, F., *Brit. J. Radiol.*, **27**, 463–66 (1954)
36. Patt, H. M., Clark, J. W., and Vogel, H., *Proc. Soc. Exptl. Biol. Med.*, **84**, 189–93 (1953)
37. Hirsh, H. M., *Radiation Research*, **5**, 9–24 (1956)
38. Clark, A. M., and Herr, E. B., *Radiation Research*, **2**, 538–543 (1955)
39. Betz, H., *Acta Unio Intern. contra Cancrum*, **7**, 814 (1952)
40. Charlier, R., *Proc. Soc. Exptl. Biol. Med.*, **86**, 290–93 (1954)
41. Gerebtzoff, M. A., and Bacq, Z. M., *Experientia*, **10**, 341–43 (1954)
42. Bacq, Z. M., Beaumariage, M. L., and Fischer, P., *J. Physiol. (London)*, **126**, 15p–16p (1954)
43. Maisin, J., Mandart, M., Lambert, G., and Maisin, H., *Compt. rend. soc. biol.*, **147**, 362–64 (1953)
44. Baldini, G., and Ferri, L., *Radiotherap., radiol. e fis. med.*, **11**, 125–145 (1955)
45. Bacq, Z. M., Fischer, P., and Beaumariage, M., *Bull. acad. med. Belg.*, **19**, 399–422 (1954)
46. Bacq, Z. M., *Brit. J. Med.*, **4983**, 39–40 (1956)
47. Fischer, P., *Arch. intern. physiol. biochim.*, **63**, 134–5 (1955)
48. Maisin, J., Maisin, H., Dunjic, A., and Maldague, P., *J. belg. de radiol.*, **38**, 394–429 (1955)
49. Maisin, H., and Fievez, C., *Proc. Radiobiol. Symposium, Liége* (Butterworth Scientific Publications, London, England, 362 pp., 1955)
50. Jennings, F. L., and Tessmer, C., *Abstract 119, Radiation Research Soc. Meeting*, (May 1956)
51. Bacq, Z. M., Deschamps, G., Fischer, P., Herve, A., Le Bihan, H., Lecomte, J., Pirolte, M., and Rayst, P., *Science*, **117**, 633–36 (1953)
52. Lamerton, L. F., Elson, L. A., and Christenson, W. R., *Brit. J. Radiol.*, **26**, 510–18 (1953)
53. Kaplan, W. D., and Lyon, M. F., *Science*, **118**, 776–78 (1953)
54. Williams, R. B., *Federation Proc.*, **13**, 446 (1954)
55. Desaive, P., and Varetto-Denoël, J., *Experientia*, **11**, 242–8 (1955)
56. Maisin, J., Maisin, H., and Dunjic, A., *Proc. Radiobiol. Symposium Liége* (Butterworth Scientific Publications, London, England, 362 pp., 1955)
57. Maisin, J., Maisin, H., and Dunjic, A., *Compt. rend. soc. biol.*, **148**, 1293–97 (1954)
58. Bacq, Z. M., and Herve, A., *Compt. rend. soc. biol.*, **149**, 1509–12 (1955)
59. Dunjic, A., Maisin, H., and Maisin, J., *Compt. rend. soc. biol.*, **169**, 1684–87 (1955)
60. Bacq, Z. M., *Acta Radiol.*, **41**, 47–55 (1954)
61. Rugh, R., and Clugston, H., *Radiation Research*, **1**, 437–47 (1954)
62. Gros, C. M., Mandel, P., and Rodesch, J., *Compt. rend.*, **236**, 2010–12 (1953)
63. Fischer, P., *Arch. intern. physiol.*, **62**, 134–36 (1954)
64. Höhne, G., Jaster, R., and Künkel, H. A., *Klin. Wochschr.*, **33**, 907–8 (1955)
65. Peterson, D. F., Fitch, F. W., and DuBois, K. P., *Proc. Soc. Exptl. Biol. Med.*, **88**, 394–97 (1955)

66. Nelson, A., *Acta Radiol.*, **42**, 485–93 (1954)
67. McDonald, J. E., *Arch. Ophthalmol.*, **51**, 201–10 (1954)
68. Fischer, M. A., Coulter, E. P., and Costello, M. J., *Proc. Soc. Exptl. Biol. Med.*, **83**, 266–68 (1953)
69. Betz, E. H., *Compt. rend. soc. biol.*, **148**, 1915–18 (1954)
70. Feinstein, R. N., and Cotter, G. J., *Science*, **118**, 552 (1953)
71. Odeblad, E., *Acta Radiol.*, **40**, 493–99 (1953)
72. Rugh, R., and Clugston, H., *Science*, **123**, 28–29 (1956)
73. Hofman, D., *Strahlentherapie*, **96**, 396–402 (1955)
74. Bacq, Z. M., and Herve, A., *Concours Med.*, **77**, 953–6 (1955)
75. Herve, A., *Bruxelles Med.*, **35**, 842–52 (1955)
76. Baldini, G., and Ferri, L., *J. Clin. Med.*, **36**, 49–61 (1955)
77. Court-Brown, W. M., *Brit. J. Radiol.*, **28**, 325–6 (1955)
78. Silverman, A., Klingerman, M. M., Fertig, J. W., and Ellis, K., *Radiology*, **66**, 403–7 (1956)
79. Sicher, K., *Brit. J. Radiol.*, **28**, 620–2 (1955)
80. Brohult, A., and Holmberg, J., *Nature*, **714**, 1102–03 (1954)
81. Deuel, H. J., Jr., Cheng, A. L., Kryder, G. D., and Bingemann, M. E., *Science*, **117**, 254–55 (1953)
82. Cheng, A. L., Ryan, M., Alfin-Slater, R., and Deuse, H., Jr., *J. Nutrition*, **52**, 637–43 (1954)
83. Cheng, A. L., Alfin-Slater, R., and Deuel, H., Jr., *J. Nutrition*, **54**, 201–07 (1954)
84. Lacassagne, A., Duplan, J. F., and Buu-Hoi, N. P., *J. Nat. Can. Inst.*, **15**, 915–21 (1955)
85. Duplan, J. F., and Rosenberg, A. J., *Compt. rend.*, **239**, 116–17 (1954)
86. Langendorff, H., and Koch, R., *Strahlentherapie*, **98**, 245–54 (1955)
87. Detrick, L. E., Debley, V., and Haley, T. J., *J. Am. Pharm. Assoc.*, **43**, 449–52 (1954)
88. Stroud, A. M., Brues, A. M., and Summers, M. N., *J. Nat. Can. Inst.*, **15**, 1109–23 (1955)
89. Rowen, M., Moos, W. S., and Samter, M., *Proc. Soc. Exptl. Biol. Med.*, **88**, 548–50 (1955)
90. Yaoi, H., and Kimura, Y., *Arch. ges. Virusforsch*, **6**, 118–23 (1955)
91. Edlund, T., *Nature*, **174**, 1102 (1954)
92. Brohult, A., and Holmberg, J., *Nature*, **174**, 1102–03 (1954)
93. Becker, J., and Kirchberg, H., *Strahlentherapie*, **98**, 343–7 (1955)
94. Maurer, H., *Strahlentherapie*, **96**, 625–8 (1955)
95. Laurell, G., and Philipson, L., *Acta Pathol. Microbiol. Scand.*, **38**, 58–68 (1956)
96. Haley, T. J., Heglin, J., and McCulloh, E., *Radiation Research*, **1**, 176–79, (1954)
97. Haley, T. J., and Rhodes, B. M., *Scien e*, **117**, 139–40 (1953)
98. Burnett, W. T., Jr., Burke, A. W., Jr., and Upton, A. C., *Am. J. Physiol.*, **174**, 254–58 (1953)
99. Barlöw, J. C., and Sellers, E. A., *Radiation Research*, **2**, 461–66 (1955)
100. Betz, E. H., *Ann. endocrinol.* (Paris), **16**, 146–51 (1955)
101. Hoene, R., Rindani, T. H., and Michon, J., *Rev. can. biol.*, **13**, 11–17 (1954)
102. Herve, A., *Arch. intern. physiol. biochim.*, **63**, 136–7 (1955)
103. Mirand, E. A., and Lasser, E. C., *Exptl. Med. & Surb.*, **13**, 234–42 (1955)

104. Baxter, H., Randall, R. G., McMillan, G. C., Drummond, J. A., and Mackenzie, K. A., *Plastic and Reconstructive Surg.*, **16**, 387–91 (1955)
105. Mücke, D., Morczek, A., and Mischel, W., *Strahlentherapie*, **97**, 473–88 (1955)
106. Bond, V. P., Skeggs, H. R., MacRae, G. D. E., Wright, L. D., Rosenblum, C., and Cronkite, E. P., *Proc. Soc. Exptl. Biol. & Med.* (To be published)
107. Haley, T. J., McCulloh, E. F., and McCormick, W. G., *Science*, **119**, 126–27 (1954)
108. Buchanan, D. J., Pearson, W. N., Amarasingham, C., Hudson, G. W., and Darby, W. J., *Am. J. Physiol.*, **175**, 437–39 (1953)
109. Cohen, L., *Brit. J. Radiol.*, **26**, 271 (1953)
110. Arons, I., Freeman, J., Sokoloff, B., and Eddy, W. H., *Brit. J. Radiol.*, **27**, 583–85 (1954)
111. Arons, I., Freeman, J., Sokoloff, B., and Eddy, W. H., *Brit. J. Radiol.*, **27**, 642–44 (1954)
112. Arons, I., Freeman, J., Sokoloff, B., and Eddy, W. H., *Brit. J. Radiol.*, **27**, 696–98 (1954)
113. Andrews, H., and Liljegren, E. J., *Am. J. Physiol.*, **183**, 322–4 (1955)
114. Burdick, F. H., *Current Researches Anesthesia & Analgesia*, **32**, 319–28 (1953)
115. Gros, C. M., and Comsa, J., *Compt. rend.*, **239**, 832–34 (1954)
116. Shapiro, N. I., Nuzhdin, N. I., and Kuzin, A. M., *Sbornik Rabot Radiobiol.*, 16–50, Akad. Nauk S.S.S.R. (Inst. Genet., Biofiz. 1955)
117. Parr, W., O'Nell, T., Bush, S., and Krebs, A. T., *Science*, **119**, 415–16 (1954)
118. Blount, H. C., Jr., *Radiology*, **65**, 250–52 (1955)
119. Bacq, Z. M., and Herve, A., *Arch. intern. physiol.*, **61**, 433–34 (1953)
120. Bonet-Maury, P., and Patti, F. J., *Radiol. et Electrol.*, **35**, 851–53 (1954)
121. Konecci, E. B., Taylor, W. F., and Wilks, S. S., *Radiation Research*, **3**, 157–64 (1955)
122. Haley, T. J., McCormick, W. G., and McCulloh, E. F., *Proc. Soc. Exptl. Biol. Med.*, **88**, 475–77 (1955)
123. Lacassagne, A., Duplan, J. F., and Buu-Hoi, N. P., *Compt. rend.*, **238**, 1279–81 (1954)
124. Kelley, B., Simmons, M. R., Day, P. L., Meschan, I., and Douglass, C. D., *Proc. Soc. Exptl. Biol. Med.*, **85**, 460–64 (1954)
125. Feinstein, R. N., Cotter, G. J., and Hampton, M. N., *Am. J. Physiol.*, **177**, 156–60 (1954)
126. Tenchov, G., Baluev, S., and Sakhatchiev, A., *Vestnik Rentgenol. i Radiol.*, **4**, 14–21 (1955)
127. Stender, H. S., and Hornykiewytsch, T., *Strahlentherapie*, **96**, 445–52 (1955)
128. Stender, H. S., and Hornykiewytsch, T., *Strahlentherapie*, **96**, 453–57 (1955)
129. Rambach, W. A., Alt, H. L., and Cooper, J. A. D., *Proc. Soc. Exptl. Biol. Med.*, **86**, 159–61 (1954)
130. Conger, A. D., *Radiology*, **66**, 63–68 (1956)
131. Howard-Flanders, P., and Wright, E. A., *Nature*, **175**, 428–29 (1955)
132. Howard-Flanders, P., Moore, D., and Wright, E. A., *Progress in Radiobiology*, pp. 456–60 (Mitchell, J. S., Holmes, B. E., and Smith, C. L., Eds., Oliver and Boyd, London, England, 1956)
133. O'Brien, J. P., Frank, E. J., and Garner, J. L., *Science*, **122**, 1140 (1955)

134. Allen, F. M., *Am. J. Roentgenol. Radium Therapy Nuclear Medicine*, **73**, 70–80 (1955)
135. Hajdukovic, S., *Acta Radiol.*, **44**, 249–56 (1955)
136. Hornsby, S., *Nature*, **178**, 87 (1956)
137. Cole, L. J., and Ellis, M. E., *Am. J. Physiol.*, **175**, 429–36 (1953)
138. Gros, C. M., and Comsa, J., *Compt. rend.*, **236**, 1611–13 (1953)
139. Burnett, W. T., and Doherty, D. G., *Radiation Research* (In press)
140. Lothe, F., and Devik, F., *Acta Radiol.*, **44**, 306–12 (1955)
141. Bond, V. P., and Carter, R. E., *Federation Proc.*, **13**, 424 (1954)
142. Hollaender, A., and Kimball, R. F., *Nature*, **177**, 726–30 (1956)
143. Devik, F., and Lothe, F., *Acta Radiol.*, **44**, 243–48 (1955)
144. Riley, H. P., *Am. J. Botany*, **42**, 765–69 (1955)
145. Brecher, G., Cronkite, E. P., and Peers, J. H., *J. Nat. Can. Inst.*, **14**, 159–75 (1953)
146. Finerty, J. C., Binhammer, R. T., Schneider, M., and Cunningham, A. W. B., *J. Nat. Can. Inst.*, **14**, 149–58 (1953)
147. Bennett, L. R., Chastain, S. M., Flint, J. S., Hansen, R. A., and Lewis, A. E., *Radiology*, **61**, 411–19 (1953)
148. Mitchell, J. S., *Brit. J. Cancer*, **7**, 313–28 (1953)
149. Jolles, B., and Laws, J. O., *Brit. J. Cancer*, **8**, 513–21 (1954)
150. Mitchell, J. S., *Brit. Med. J.*, **I**, 39–40 (1956)
151. Gerschman, R., Gilbert, D. L., Nye, S. W., Dwyer, P., and Fenn, W. O., *Science*, **119**, 623–26 (1954)
152. Gerschman, R., Gilbert, D. L., Nye, S. W., and Fenn, W. O., *Proc. Soc. Exptl. Biol. Med.*, **86**, 27–29 (1954)
153. Cronkite, E. P., and Brecher, G., *Ann. N. Y. Acad. Sci.*, **59**, 815–33 (1955)
154. Jacobson, L. O., Marks, E. K., Gaston, E. O., Simmons, E. L., and Robson, M. L., *Bull. N. Y. Acad. Med.*, **30**, 675–92 (1954)
155. Jacobson, L. O., *Am. J. Roentgenol. Radium Therapy Nuclear Medicine*, (Janeway Lecture), **72**, 543–55 (1954)
156. Maisin, J., Maisin, H., Dunjic, A., and Maldague, P., *Proc. Intern. Conf. Peaceful Uses Atomic Energy*, pp. 315–29 (United Nations, New York, N. Y., 402 pp., 1956)
157. Hilfinger, M. F., Sr., Ferguson, J. H., and Riemenscheider, P. A., *J. Lab. Clin. Med.*, **42**, 581–91 (1953)
158. Schlang, H. A., Cronkite, E. P., and Brecher, G., (Lecture and Review Series No. 53-1. Naval Med. Research Inst., Bethesda, Md., 1953)
159. Lorenz, E., and Congdon, C. C., *J. Nat. Can. Inst.*, **14**, 955–64 (1954)
160. Congdon, C. C., and Lorenz, E., *Am. J. Physiol.*, **176**, 297–300 (1954)
161. Cole, L. J., Habermeyer, J. G., and Bond, V. P., *J. Nat. Can. Inst.*, **16**, 1–9 (1955)
162. Hirsch, B. B., Brown, M. B., Nagareda, C. S., and Kaplan, H. S., *Radiation Research*, **5**, 52–57 (1956)
163. Ellinger, F., *Radiol. Clin.*, **23**, 229–39 (1954)
164. Goldwasser, E., and White, W. F., *Proc. Intern. Conf. Peaceful Uses Atomic Energy*, pp. 343–45 (United Nations, New York, N. Y., 402 pp., 1956)

165. Smith, F., Smith, W. W., Andrews, H. L., and Grenan, M. M., *Am. J. Physiol.*, **182,** 396–99 (1955)
166. Jacobson, L. O., Marks, E. K., and Gaston, E. O., *Proc. Soc. Exptl. Biol. Med.*, **91,** 135–39 (1956)
167. Bohr, D. F., Rondell, P. A., Palmer, L. E., Baker, B. L., and Bethell, F. H., *Am. J. Physiol.*, **183,** 331–34 (1935)
168. Bohr, D. F., Rondell, P. A., Palmer, L. E., and Bethell, F. H., *Am. J. Physiol.*, **183,** 335–39 (1935)
169. Jacobson, L. O., Simmons, E. L., Marks, E. K., Gaston, E. O., Robson, J. M., and Eldridge, J. H., *J. Lab. & Clin. Med.*, **37,** 683–688 (1951)
170. Saleeby, E. R., *Am. J. Path.*, **I,** 69–77 (1925)
171. Allen, B. R., Wardell, H. G., and Clay, M., *Science*, **123,** 1080 (1956)
172. Cole, L. J., and Ellis, M. E., *mA. J. Physiol.*, **173,** 487–94 (1953)
173. Cole, L. J., Fishler, M. C., and Bond, V. P., *Proc. Nat. Acad. Sci.*, **39,** 759–72 (1953)
174. Cole, L. J., and Ellis, M. E., *Radiation Research*, **1,** 128–29 (1954)
175. Cole, L. J., and Ellis, M. E., *Radiation Research*, **1,** 347–57 (1954)
176. Fishler, M. C., Cole, L. J., Bond, V. P., and Milne, W. L., *Am. J. Physiol.*, **177,** 236–42 (1954)
177. Cole, L. J., and Ellis, M. E., *Fundamentals of Radiobiology*, Bacq., Z. M., and Alexander, P., Eds. (Butterworth Scientific Publications, London, England, 389 pp., 1955)
178. Cole, L. J., Fishler, M. C., and Ellis, M. E., *Radiology*, **64,** 201–7 (1955)
179. Main, R. K., Cole, L. J., and Bond, V. P., *Arch. Biochem. Biophys.*, **56.**
180. Cole, L. J., and Ellis, M. E., *Cancer Research*, **14,** 738–44 (1954)
181. Congdon, C. L., McKinley, S. H., and Urso, P., Jr., *Radiation Research*, **4,** 424–434 (1956)
182. Swift, M. N., Taketa, S., Bond, V. P., *Radiation Research*, **4,** 186–92 (1956)
183. Maisin, J. H., Maisin, H. E., and Dunjic, A., *Compt. rend. soc. biol.*, **148,** 743–45 (1954)
184. Ungar, G., Damgaard, E., and Williams, F., *J. Appl. Physiol.*, **8,** 287–8 (1955)
185. Finerty, J. C., Binhammer, R. T., and Schneider, M., *Science*, **118,** 654–55 (1953)
186. Schneider, M., Wybourn, R. C., Binhammer, R., and Finerty, J. C., *Radiology*, **62,** 234–40 (1954)
187. Binhammer, R. T., Schneider, M., and Finerty, J. C., *Am. J. Physiol.*, **175,** 440–42 (1953)
188. Metz, G., Binhammer, R. T., Schneider, M., and Finerty, J. C., *Radiation Research*, **2,** 159–65 (1955)
189. Binhammer, R. T., Metz, G., Schneider, M., and Finerty, J. C., *Arch. Pathol.*, **59,** 594–606 (1955)
190. Genaud, P. E., and Meot, R., *Compt. rend. soc. biol.*, **236,** 2004–6 (1953)
191. May, R. M., Arpiarian, N., *Compt. rend. soc. biol.*, **239,** 1151–53 (1954)
192. Maisin, J., Van Lancker, J., Dunjic, A., Lambert, G., and Passeau, L., *Compt. rend. soc. biol.*, **147,** 1517–20 (1953)
193. Van Lancker, J., *Compt. rend. soc. biol.*, **147,** 1513–15 (1953)

194. Van Lancker, J., *Compt. rend. soc. biol.*, **147**, 1515–17 (1953)
195. Maisin, J., Dunjic, A., Van Lancker, J., Lambert, G., and Passeau, L., *Compt. rend. soc. biol.*, **147**, 1520–22 (1953)
196. Maisin, J. H., Dunjic, A., and Maisin, H. E., *Compt. rend. soc. biol.*, **148**, 611–15 (1954)
197. Maisin, J. H., Van Lancker, J., Lambert, G., Passeau, L., Mandart, M., Dunjic, A., and Maisin, H., *Acta Radiol.* Suppl. **116**, 40–8 (1954)
198. Maisin, J., Maisin, H., and Dunjic, A., *Proc. Radiobiol Symposium, Liége* pp. 154–69, (Bacq. Z. M., and Alexander P., Eds. Butterworth Scientific Publications, London, England, 1955)
199. Maisin, J., Maisin, H., Dunjic, A., and Maldague, P., *Bull. acad. Suisse sci. Med.*, **11**, 247–73 (1955)
200. Maisin, J., Maisin, H., Dunjic, A., and Maldague, P., *Compt. rend. soc. biol.*, **149**, 833–36 (1955)
201. Bond, V. P., Silverman, M. S., and Cronkite, E. P., *Radiation Research*, **1**, 389–400 (1954)
202. Quastler, H., *Radiation Research*, **4**, 303–20 (1956)
203. Swift, M. N., and Taketa, S. T., *Am. J., Am. J. Physiol.*, **185**, 85–91 (1956)
204. Lamerton, L. F., Elson, L. A., Harriss, E. B., and Christenson, W. R., *Brit. J. Radiol.*, **26**, 568–76 (1953)
205. Lamerton, L. F., Elson, L. A., and Harriss, E. B., *Brit. J. Radiol.*, **126**, 568–76 (1953)
206. Lamerton, L. F., and Baxter, C. F., *Brit. J. Radiol.*, **28**, 87–94 (1955)
207. Baxter, C. F., Belcher, E. H., Harriss, E. B., and Lamerton, L. F., *Brit. J. Hematol.*, **1**, 86–102 (1955)
208. Kereiakes, J. G., Parr, W. G., Storer, J. B., and Krebs, A. T., *Proc. Soc. Exptl. Biol. Med.*, **86**, 153–56 (1954)
209. Swift, M. N., Taketa, S. T., and Bond, V. P., *Radiation Research*, **1**, 241–52 (1954)
210. Brown, M. B., Hirsch, B. B., Nagareda, C. J., Hochstetler, S. K., Faraghan, W. G., Toch, P., and Kaplan, H. S., *J. Nat. Can. Inst.*, **15**, 949–73 (1955)
211. Duplan, J. F., *Compt. rend. soc. biol.* (To be published 1956)
212. Barnes, D. W. H., and Loutit, J. F., *Proc. Roy. Soc. Med.*, **46**, 251–2 (1953)
213. Loutit, J. F., *J. Nuclear Energy*, **1**, 87–91 (1954)
214. Barnes, D. W. H., and Loutit, J. F., *Nucleonics*, **12**, 68–71 (1954)
215. Barnes, D. W. H., and Loutit, J. F., *J. Nat. Can. Inst.*, **15**, 901–5 (1955)
216. Barnes, D. W. H., and Loutit, J. F., *Proc. Intern. Conf. Peaceful Uses Atomic Energy*, pp. 291–96 (United Nations, New York, N. Y., 1956)
217. Lorenz, E., and Congdon, C. C., *Ann. Rev. Med.*, **5**, 323–38 (1954)
218. Booz, G., *Compt. rend. soc. biol.*, **149**, 1294–96 (1955)
219. Betz, E. H., Booz, G., and Firket, J., *Proc. Intern. Conf. Peaceful Uses Atomic Energy*, pp. 297–302 (United Nations, New York, N. Y., 402 pp., 1956)
220. Stohlman, F., Jr., Cronkite, E. P., and Brecher, G., *Proc. Soc. Exptl. Biol. Med.*, **88**, 402–6 (1955)
221. Stohlman, F., Jr., and Brecher, G., *Proc. Soc. Exptl. Biol. Med.*, **91**, 1–4 (1956)
222. Savitsky, J. P., *Blood*, **10**, 52–61 (1955)

223. Hale, W. M., and Stoner, R. D., *Radiation Research*, **1**, 459–69 (1954)
224. Brown, J. R. C., *Science*, **121**, 511–12 (1955)
225. Miller, C. L., *Nature*, **178**, 142 (1956)
226. Lindsley, D. L., Odell, T. T., Jr., and Tausche, F. G., *Proc. Soc. Exptl. Biol. Med.*, **90**, 512–15 (1955)
227. Ford, C. E., Hamerton, J. L., Barnes, D. W. H., and Loutit, J. F., *Nature*, **177**, 452–54 (1956)
228. Nowell, P. C., Cole, L. J., Habermeyer, J. G., and Roan, P. L., *Cancer Research*, **16**, 258–61 (1956)
229. Makinodan, T., *Proc. Soc. Exptl. Biol. Med.*, **92**, 174–79 (1956)
230. Jaroslow, B. N., and Taliaferro, W. H., *J. Infectious Diseases*, **98**, 75–81 (1956)

COMPARATIVE PHYSIOLOGY: OSMOTIC AND IONIC REGULATION IN AQUATIC ANIMALS[1]

By L. C. Beadle

Department of Zoology, Makerere University College, Kampala, Uganda, East Africa

Introduction

The subject may be defined as the study of the means by which aquatic animals regulate their intra- and extra-cellular fluids with respect to water and salts to maintain their tissues in a proper functioning condition in environments which may be both unfavourable and fluctuating. It must also include the regulatory mechanisms of those animals which have no extracellular body fluids such as Protozoa and Coelenterates. Regarded from an evolutionary standpoint we have here one aspect of the progressive emancipation from the shackles of the environment. This aspect is of fundamental interest to the comparative physiologist and will be stressed in this review. The boundaries of the subject are rather arbitrary and no claim can be made to completeness. The outlook and scope will necessarily be determined in some measure by the interests and limitations of the reviewer.

Since it is the first review of this subject to appear in this annual, I propose to pick up the threads from the rather more distant past than is customary with topics which are regularly reviewed. As a starting point I take the publication of Krogh's book in 1939 (1). For work done up to that time the reader is referred also to reviews by Schlieper (2, 3), Smith (4), Pantin (5) and Beadle (6). Prosser (7, chapters 3 and 4) reviewed much of the literature up to 1949 and presented the analytical data in a useful tabular form. Specific reference to an author before 1939 will occasionally be made when it appears that the significance of subsequent work is thereby made clearer.

By the late 1930's enough was known of the composition of the body fluids in relation to the environment to give a general picture of the osmotic and ionic levels of the main groups of animals. The site of the regulatory mechanisms had in many cases been located. Nagel (8) had demonstrated the active uptake of ions in *Carcinus moenas* and Krogh had just shown that this was an important component of the osmoregulatory mechanism of many freshwater animals (1). Much of the chemical data was, however, not very accurate and many animals were too small for the analytical methods then available, and there was little reliable information concerning the osmotic and ionic relations between tissue cells and body fluids.

The animal groups which have been selected are those on which work has been done during the period under review.

[1] The survey of literature pertaining to this review was completed in July, 1956.

Methods

Many of the recent advances have been made possible by improved and smaller scale techniques. On the conventional micro-scale the improved inorganic analytical methods used by Robertson (26, 40, 55, 56) on marine animals have yielded important information. A number of methods have been developed for estimating inorganic ions in quantities down to about 1 μg., which have been reviewed by Glick (9) and Kirk (10). Shaw (11) developed a relatively simple technique for estimation of Na, K, Ca, and Mg. In the final stage they are all titrated electrometrically as chlorides. Important results have followed from the use of the ultramicro-methods devised by Ramsay and his collaborators—simultaneous estimation of Na and K by flame photometry down to 10^{-5} μg. (12), an electrometric titration of chloride down to 10^{-4} μg. in a volume of 0.5×10^{-3} μl., Ag ions being released into the drop by passing a current through a minute silver electrode (13), and an ultramicro-method for determination of freezing point with a probable error of the equivalent of 0.01 per cent NaCl in 0.1×10^{-6} ml. of fluid (14).

Improvements in micro-manipulative skills, for extracting fluids from small spaces etc., have been equally important, as for example the ingenious techniques used by Ramsay in his work on earthworm nephridia and insect malpighian tubules (see below).

It will be seen from the following that both radioactive isotopes and heavy water have been used successfully for the small scale study of ion and water movements.

Protozoa

Owing to the technical difficulties involved we have so far practically no direct and quantitative information regarding the chemical composition of the protoplasm of any protozoal cell nor of the fluid extruded by the contractile vacuoles, where such exist. With the progressive development of ultramicro methods and the use of radioisotopes we may perhaps expect to get this information, which would very greatly increase our present scanty knowledge of the regulatory processes in these animals.

The relevant work to date has mainly centered around the mechanism and function of the contractile vacuole. Reviews are to be found in Krogh (1) and Kitching (15, 16, 17). It has long been known that contractile vacuoles are universally present in freshwater protozoa, but are found only spasmodically in marine and parasitic forms (15). This is consistent with the idea, which might well be deduced from observation of their behaviour, that their function is to remove water entering by osmosis through the cell surfaces. It was supported by early workers who found with several species an inverse relation between external osmotic pressure and rate of vacuolar output. The discovery by Kitching (18) that 0.00001 M cyanide both inhibits vacuolar output and increases the cell volume of freshwater Peritricha and of marine forms in diluted seawater (both effects being reversible) served further to support this contention and to suggest that the energy thus expended is

derived from the oxidative mechanism of the cell. It also showed that the osmotic pressure of the cell in freshwater species is much higher than that of the medium. The latest estimate of internal osmotic pressure was made by Løvtrup & Pigon (19) on the amoeboid *Pelomyxa* by disintegration in a known volume of distilled water. Making certain corrections they arrived at an osmotic pressure equivalent to about 0.09 M nonelectrolyte. That of the culture medium was 0.007 M.

With regard to the vacuolar mechanism itself, it seems generally agreed (16) that the vacuole fills at a constant rate or even, in some instances, with acceleration. A simple osmotic theory of diastole is therefore not acceptable, though the work of Fowler (20) and Hopkins (21) on *Amoeba* suggested that osmotic forces are involved. In any case some secretory device is needed to set up an osmotic gradient and maybe to maintain it across the vacuolar membrane during diastole. In this connection the discovery of osmophil structures in or close to the vacuolar membrane of many, but not all kinds of protozoa (they have never been found in Rhizopoda) is of interest (16). Whether these structures are related to the osmophil Golgi bodies of animal cells, for which there is good evidence for a connection with secretion, is doubtful, but there is certainly a problem here for investigation. The mechanism of systole is also unsolved though experiments by Kitching (22, 23, 24) on the effects of sudden changes of temperature and of applied hydrostatic pressure led him to the conclusion that vacuolar contraction is unconnected with the turgor of the whole cell but is done by the vacuolar membrane itself which is probably composed of orientated and contractile protein molecules, and might at the same time be the site of a secretory mechanism functioning according to the theory of Goldacre (25).

The permeability to water of the cell surface of *Pelomyxa* was estimated by Løvtrup & Pigon (19) using heavy water and by measuring the resulting weight changes in a Cartesian diver. The permeability constant worked out at 0.011 μ^3/μ^2/atm. min., which is low but within the range of values estimated for other animal cells. We have no information regarding permeability to ions nor direct evidence for active uptake, though we should suspect this to take place.

Coelenterata

These are multicellular aquatic animals lacking an extracellular fluid and, so far as we know, any localised organs for excretion or for absorbtion from the external medium. The majority of their cells are exposed either directly to the water (ectoderm) or to the fluid in the enteron which is open to the exterior (endoderm). These two layers are separated by a gelatinous mesogloea which is a structureless layer in the hydroid but voluminous in the medusoid forms and might be regarded in some respects as a "body fluid." The vast majority are marine but some inhabit brackish waters (e.g., *Clava* and *Cordylophora*) and a very few are adapted to freshwater (e.g., *Hydra* and the medusoid *Limnocnida*).

The large marine medusae (Scyphozoa) such as *Aurelia* and *Cyanea* have been chemically analysed several times and the early work was reviewed by Krogh (1). The main conclusions were that, regarding total osmotic pressure, they are isotonic with the seawater but that some ionic regulation renders the internal sulphate lower and the potassium higher than in the external medium.

More critical results were obtained by Robertson (26) on *Aurelia aurita* with improved methods of analysis and by removing the cells whose disintegration he showed was partly responsible for the high potassium figures of the earlier workers. He further compared the ionic composition of the fluid got directly from the mesogloea with that of the same fluid dialysed against seawater. This would show what differences between internal and external media must be attributed to factors other than a simple Donnan equilibrium. He found in fact that none of the ions investigated were in true equilibrium and interpreted his findings as showing that the regulatory mechanism involves the active elimination of SO_4 and accumulation of K by the epithelium bounding the mesogloea "with resultant alteration in the remaining ions in conformity with the osmotic equilibrium between the jelly and seawater." The freshwater medusae, which are both small and difficult to obtain, have not yet been examined.

No work has been done on the permeability of marine medusae but Hosoi (27) measured the water and calcium content of the tissues of three sea anemones in normal, dilute, and concentrated seawater. As would be expected the permeability to water is high, but he also concluded from his results that the tissues were moderately permeable to calcium, though there was no evidence for active regulation of this ion.

Since the mesogloea of the nonmedusoid Coelenterates is insignificant in volume, the work done on these was necessarily concerned mainly with the relation between the composition of the cellular tissues and that of the environment. Palmhert (28) studied survival and changes in weight of the freshwater *Pelmatohydra* and *Chlorohydra* in water with added seawater. They survived in salinities up to about 2 per cent (equivalent to 0.035 M NaCl) and a weight decrease was first detected in 1.5 per cent (0.025 M NaCl), which was therefore concluded to be the approximate internal osmotic concentration. Lilly (29) studied the same two Hydras in sucrose solutions and found that both cell layers are highly permeable to water. Measurements of volume in a range of concentrations suggested that the osmotic pressure of the tissue is equivalent to about 0.04 M sucrose.

This is surprisingly in agreement with Palmhert's figure having in mind that sucrose is a nonelectrolyte. Lilly by using ^{24}Na, ^{42}K and ^{82}Br showed that *Hydra* is very permeable to these ions. They all pass readily into the animal and are actively absorbed from very low concentrations in the surrounding water. To what extent Na and K are differentially distributed between cells and mesogloea cannot of course be decided, but it must be remembered that the contractile elements in the ecto- and endoderm are placed on either side

of the mesogloea and that their contractile mechanism probably depends, as in higher animals, upon a differential distribution of these ions (17).

Active control of ions is thus demonstrated, and in fact these animals could not exist without such control. But the nature of the mechanism remains to be investigated. As pointed out by Krogh (1) and arising from the account given by Jacobs (30) there is the interesting problem of the mechanism by which the density of certain non-pneumatophoric zooids of Siphonophores is regulated, thus controlling the buoyancy of the animal. This must involve an active mechanism and, though the organs concerned are relatively large, it does not yet seem to have been investigated.

Annelida

The Polychaete worms of the family Nereidae have been a favourite material for studies of osmotic regulation (1). Most are marine, but *Nereis diversicolor* is found in estuaries and has the rudiments of a hypertonic regulating mechanism. Some other estuarine Polychaetes, such as *Arenicola marina*, have no such mechanism but can survive considerable dilution of the seawater because their tissues can still function in a much diluted body fluid. Cole (31) found that the purely marine Polychaetes *Amphitrite brunnea* and *Glycera dibranchiata* have considerable powers of ionic regulation, but unfortunately we know nothing of the ionic composition of the body fluid of the Nereids whose osmoregulatory capacities have been investigated.

Wells & Ledingham (32) found that isolated muscle from *Nereis diversicolor* could function in seawater as dilute as the least saline water in which the worm is normally found. This throws some doubt on the survival value of its powers of osmotic regulation. It may be, however, that hypertonic regulation in this animal is an accidental by-product of ionic regulation which no doubt could be shown to be in operation between water, body fluid, and tissues. *Arenicola marina* has no osmotic control but Robertson (26) showed that in dilute seawater the ionic gradients were much increased. In the body fluid the concentration of K had become 118, of Ca 113 and of SO_4 90 per cent of that of the same ions in the external 75 per cent seawater. Ionic regulation is therefore likely to play an important part in the adaptation of *Arenicola* to dilute seawater. Wells & Ledingham (32) discovered that the rate of dilution of the body fluid is critical in the adaptation of Polychaetes to lowered salinity. Muscular activity can be maintained as long as dilution is slow enough and proceeds exponentially. In nature the rate of osmotic uptake of water is controlled by the body wall.

Fretter (33) by using ^{24}Na measured the exchange of sodium between body fluid and seawater in *Nereis diversicolor* and demonstrated an exchange through the body wall in both full strength and dilute seawater. A much more rapid exchange takes place with *Perinereis cultrifera* which is a purely marine species and presumably more permeable. Oxygen deficiency increased the rate of exchange in *N. diversicolor*. It is difficult to find any good evidence for what the author explicitly set out to find, but drew no conclusions thereon

at the end, that *N. diversicolor* maintains a hypertonic body fluid in dilute seawater by an active uptake of ions which *P. cultrifera* cannot do.

Much more could be learned of the regulating mechanisms in these Polychaetes by analysis of the ionic relations between water, body fluid, blood, tissues, and urine and of the changes in these relations resulting from dilution of the seawater. Methods are now available even for blood and urine, which have been neglected in the past owing to technical difficulties.

Bogucki (34) cultured *N. diversicolor* in Baltic seawater of 7 per cent salinity and subjected various developmental stages to further dilution. Pre-larval and larval stages were most sensitive to this treatment. The most resistant were young worms, some of which actually survived for several months in freshwater, but adults were not so resistant. These very interesting findings should be amplified by a chemical analysis of the developing regulatory mechanism. Indeed they suggest a new field of investigation into the "embryology" of osmotic and ionic regulation.

The Oligochaeta include many freshwater and a few saline water worms none of which has been investigated. But work has been done on two species of earthworms which in fact can only live in contact with soil water and will survive indefinitely immersed in aerated freshwater. Bahl (35) using relatively crude methods on *Pheretima posthuma* found by measurement of freezing points that the urine was strongly hypotonic to both blood and body fluid. Ramsay (36) with more delicate methods on *Lumbricus terrestris* in freshwater found that the mean concentration of the body fluid was equivalent to 0.53 per cent NaCl, that the blood is slightly hypotonic to this, and that the urine is very hypotonic (mean equivalent to 0.1 per cent NaCl). It has no osmotic control in water of increased salinity. He also measured the freezing points of the fluid in different regions of the nephridium and found clear evidence of a salt reabsorbing mechanism localised in the wide section of the tube (37). He pointed out the analogy between this mechanism and that of the vertebrate nephron. It might be added that a similar salt reabsorbing section was found and its function demonstrated in the antennal glands of the freshwater crayfish *Potomobius astaeus* by Peters (38). The pattern of osmotic regulation in the earthworm is thus typical of most freshwater animals.

The work of Winterstein & Özer (39) on the effect of osmotic pressure and ionic changes on the contraction of the isolated dorsal musculature of the leech *Hirudo medicinalis*, though not directly concerned with the animal's regulatory mechanism, would be important to any worker who investigated it.

Crustacea

More work has been done on this than on any other invertebrate group partly because it includes animals such as crabs which are large enough to apply chemical analytical methods relatively crude by modern standards. They are also interesting because they are by origin marine and have become

adapted to all the major types of aquatic environment; brackish water, freshwater and inland saline water. Some are amphibious and a few, such as the porcellionid woodlice, are fully adapted to land life. The subject was extensively reviewed by Krogh in 1939 (1). In general the largest species belong to the most highly evolved groups and for this reason most of our knowledge has been got from the Decapoda (Lobsters, Crabs etc.). The calcified integument of these is of very low permeability but the gills present a large surface through which important changes occur between blood and external medium. The excretory organs (antennary glands) are large enough for chemical investigation on the ordinary micro scale.

Most of the purely marine crustacea so far investigated have blood practically isotonic with seawater. Certain grapsoid crabs are exceptional in having a definitely hypotonic blood (1, 54). Robertson (55) has confirmed this with *Pachygrapsus marmoratus* whose blood concentration he estimated to be about 90 per cent of that of seawater. He also confirmed and extended the conclusions of previous workers that, even in those crabs where the blood is in osmotic equilibrium with the seawater the concentrations of individual ions are regulated to a considerable extent. Thus, in *Homarus* and *Cancer* the blood contains more Na, K, and Ca and less Cl, Mg, and SO_4 than seawater, the reverse relation being found between urine and blood (56). Analyses of the blood of eight marine Decapoda together with the Stomatopod *Squilla mantis* showed that all ions are regulated but to very different extents in the different species. The greatest difference was found with Mg which varied according to the species from about 15 to 100 per cent of that in seawater. Robertson found that in general the most active species maintained the lowest Mg level, and he referred in this connection to the depressing action of the Mg ion on neuromuscular transmission and to the use of Mg salts as narcotics (55). More work is needed on this subject, but it is clear that in marine crabs there are at least two sets of active processes at work, in the gills and in the excretory organs, which are responsible for the ionic imbalance between blood and seawater. It is not difficult to imagine adjustments in the rates of these processes whereby hypo- or hypertonic regulation could evolve in the appropriate environments.

Regulation in the brackish water crab *Carcinus moenas* has been the subject of many investigations (1). In seawater the blood is isotonic and becomes progressively more hypertonic as the seawater is diluted, but it cannot live indefinitely in seawater diluted to much less than 40 per cent. In all dilutions the excretory organs produce a urine which is isotonic with the blood and therefore do not play a direct part in osmoregulation. The blood level is maintained even in starved animals. Shaw (57) found that the blood Na, Cl, and K, after an initial fall, are maintained at a relatively constant level when the seawater is diluted from 80 to 40 per cent. Within these limits the regulatory mechanism is very efficient. Some details of ionic regulation in *Carcinus* were disclosed by Webb (58). Though the blood is isotonic with seawater active processes at the gill surface result in accumulation of Na, K,

Ca, and Cl and the antennary glands function to conserve K and to eliminate Mg and SO_4 so that the ionic composition of the blood differs considerably from the same blood in dialysis equilibrium with seawater. There being no osmotic gradient across the gill surface, it has been concluded that water must be actively taken up to compensate for loss in the urine. Webb developed the thesis that in dilute seawater osmotic regulation is brought about by the suspension of active water uptake and by an intensification of the active processes in the gills and excretory organs which are responsible for ionic regulation.

The japanese "Woolhanded Crab" *Eriocheir sinensis* represents another evolutionary stage in that it is fully adapted to freshwater in which its blood is necessarily hypertonic; but it returns to breed in seawater in which its blood is slightly hypotonic. Here again the urine, even in freshwater, is isotonic with the blood, but the gills readily absorb ions from both dilute seawater and freshwater. Ionic regulation is considerable and is especially evident with Mg which is actively excreted in seawater and conserved in freshwater (1).

Koch & Heuts (59) studied the osmotic pressure and chloride of the blood and water when the salinity of the latter is raised from fresh to seawater. Both are remarkably constant until the osmotic pressure of the water is raised to that of the blood (about 23 per 1000) above which both begin to rise. Their observation that the muscle chloride is, by comparison, only slightly raised must be accepted with caution, since we do not know what proportion, if any, of this chloride is intracellular.

The regulatory mechanism in *Eriocheir* seems therefore to resemble that of *Carcinus* but its efficiency is increased and *Eriocheir* lives successfully in freshwater. On the other hand hypertonic regulation in both the above species is by no means perfect and the blood osmotic pressure in fact drops considerably when the seawater is diluted. Since the proper functioning of tissues, especially muscle and nerve, depends upon the maintenance of certain ionic relations between the inside and outside of the cells, it is clear that the tissues of these animals must be adaptable to a considerable range in concentration and composition of the surrounding body fluid. This problem has recently been investigated in *C. moenas* by Shaw (57, 60) by the simultaneous analysis of the ionic composition of single muscle fibres and of the blood, of the total muscle ions by electrical resistance and by measurement of resting potential across the muscle cell membrane. With *Carcinus* in seawater it seems that K and Cl are passively distributed across the cell membrane and that the major active process is the pumping of Na out of the cells, which is of course the basis of the electrical activity in vertebrate muscle and nerve (41). When the seawater is diluted the muscle fibres swell through osmotic uptake of water, but the resting potential remains practically constant (*ca.* 59 mV). The ionic regulating mechanism, and particularly the "sodium pump" is so adjusted as to maintain the same ratio across the cell membrane of Na, Cl, and K as when the crab is in seawater.

The purely freshwater crabs of the Genus *Potomon* (*Telphusa*) may be regarded as yet another step in this line of evolution. The osmotic pressure of the blood is higher than that of any other known freshwater animal (*ca.* 350 mM), but it is maintained, like *Eriocheir*, with the production of an isotonic urine (1). Nothing is yet known about the ionic composition of blood, urine, or tissues. Ewer & Hattingh (61) have found with two species of *Potomon* that the four anterior but not the three posterior gills absorb and reduce silver from silver nitrate. This is taken to indicate the site of chloride absorption from the water, a technique first employed by Koch (62).

The Prawns of the sub-family Palaemoninae is another group of Crustacea which has marine, brackish, and freshwater species, some living in a great range of salinity. Pannikar (63) reviewed and extended the work on this group. The brackish prawn *Palaemonetes varians* and the marine *Leander serratus* and *Leander squilla* all maintain a blood hypertonic in dilute seawater and hypotonic in normal seawater, but the urine is always isotonic with the blood. The ionic composition of blood and urine of *L. serratus* in various concentrations of seawater was determined by Parry (64). The urine is isotonic with the blood but the blood Mg and SO_4 are low due to elimination of these by the excretory organs. Nothing is known about the blood and urine of purely freshwater prawns, but the structure of the excretory organs of the freshwater *Paleomon* is similar to that of the above three species and does not appear to be adapted to produce a hypotonic urine [Patwardhan, quoted in Pannikar (63)]. Parry (65) studied the rate of urine production by *P. varians* and discussed this in relation to what is known about other Crustacea. Urine flow is at a minimum when blood and external water are isotonic, but increases in both hypo- and hypertonic seawater. In five per cent seawater the flow (expressed as percentage of body weight per hour) is five to ten times that of the crayfish *Potamobius* and of the crab *Eriocheir sinensis* is freshwater. This suggests that full adaptation to freshwater involves some mechanism or permeability change reducing the osmotic inflow of water.

The Genus *Gammarus* (Amphipoda) is yet another group with marine, brackish, and freshwater species (66, 67, 68). The brackish species maintain a very high blood osmotic pressure in dilute seawater and *Gammarus duebeni* can do likewise even in freshwater in which it can also live. It becomes progressively more confined to freshwater from East to West of the British Isles. Beadle & Cragg (69) found that specimens taken from freshwater can retain chloride more effectively in distilled water than others from brackish water; and concluded that these are two physiological varieties. On the basis of survival in distilled water these conclusions were not supported by Hynes (68). He also found that the length of the eosinophil portion of the antennal glands, supposedly concerned with salt reabsorption, was the same in both freshwater and brackish specimens, but less than that of the freshwater *Gammarus pulex*. Urine analyses are needed to support the indications from this that *G. pulex*, but not *G. duebeni*, has developed an excretory organ

capable of producing a hypotonic urine. The low blood osmotic pressure of *G. pulex* shows that it has gone further in freshwater adaptation than *G. duebeni* (66).

The freshwater crayfish of the genera *Potamobius* and *Cambarus* are large animals completely adapted to freshwater. The regulatory mechanism involves active uptake of ions through the gills, a hypotonic urine, and the selective excretion of ions. The excretory organs have long "nephridial canals" not found in the crabs *Eriocheir* and *Potamon* whose freshwater adaptation does not involve a hypotonic urine (1). The blood osmotic pressure is much lower than that of *Potamon*, but still rather high for a freshwater animal (6). Wikgren (67) estimated that the permeability to water and chloride of *Potamobius astacus* is very low and found that at low temperatures the ion absorbing mechanism is depressed. Cole *et al.* (68, 69) found that the composition of perfusing fluids for the proper functioning of isolated hearts of the freshwater *Cambarus clarkii* and the marine lobster *Homarus americanus* must be close to the normal composition of the blood. The ranges of tolerance of changes in osmotic pressure and ionic composition were determined. This kind of experiment on the actual functional needs of tissues, as well as studies of the ionic relations of tissues and body fluids, should be extended to other animals and would yield information very relevant to this subject. McLennan (73) found that the ionic composition of the eggs of *Cambarus virilis* before laying is very different from the parent's blood and contains more K and less Na. After laying, water is absorbed but the ionic concentration is maintained, presumably by active uptake from the water.

The Cladocera are an almost exclusively freshwater group which, owing to their small size and phyllopod limbs, present a very large relative surface area to the water and would be confronted with a grave osmoregulatory problem. Krogh (1) reviewed the work of Fritsche who determined the freezing point depression of the blood of *Daphnia magna* ($\Delta 0.25°C.$) and showed that it actively absorbs salt against a gradient. He also quoted Ussing's work with heavy water showing an 80 per cent exchange in less than two minutes. Holm-Jensen (71) investigated *D. magna* with radioactive isotopes. The rates of active uptake of Na, K, Cl, and Br were determined. He also studied the uptake of the heavy metals As, Cu, Hg, and Pb and concluded that their toxic effects are primarily due to a blockage of the ion absorbing mechanism with consequent loss of salt from the blood. This result did not follow from lethal doses of a number of organic poisons.

It would be interesting to know the blood osmotic pressures of the few marine and inland saline water Cladocera. We should expect them to be maintained at the low level characteristic of freshwater animals adapted to saline water such as marine Teleosts, *Artemia salina* and certain insect larvae (6).

Some interesting experiments were done by Pannikar & Sproston (72) on two parasitic crustaceans. *Leonaeocera branchialis*, is a blood sucking parasitic Copepod from marine teleost fish of the Genus *Gadus*. So long as the

parasite is attached to the host the osmotic pressure of its body fluid (equivalent to 2.0 to 2.8 per cent NaCl) is hypotonic to the seawater (3.5 per cent NaCl). This is associated with the low osmotic pressure of the host's blood (1.4 per cent NaCl) characteristic of marine teleosts. When removed from the host it can be kept alive in seawater to which the body fluid becomes isotonic. *Bopyrus squillarum* is a blood sucking Isopod from the prawn *Leander serratus*, and in this case the body fluid is very slightly hypotonic to seawater which is no doubt associated with the slight hypotonicity of the blood of *L. serratus* in seawater (see above).

Insecta

A recent general review was written by Buck (76). We shall pick up the threads from this and extend with later developments. The most important single feature which has enabled insects so successfully to colonise dry land is the cuticle. For small animals with such a large surface area a covering of very low permeability is essential to prevent desiccation. There is little doubt that aquatic insects are descended from terrestrial forms and that secondary adaptation to water has been greatly assisted by the cuticle which can prevent, or at least much retard, the diffusion of water and salts between blood (haemolymph) and external medium.

The permeability of the cuticle of the neuropteran larva *Sialis lutaria* has recently been studied by Shaw (77). Estimated by means of D_2O the permeability to water is vastly lower than that of the integument of any nonarthropod aquatic animal, though it is more permeable than that of terrestrial insects. The permeability to Na and Cl is also extremely low and there seems little doubt that a cuticle presenting a strong barrier to the diffusion of water and ions, but not to oxygen and carbon dioxide, is a general feature of aquatic insects and enables them to expose large surface areas for respiration with little osmoregulatory inconvenience. The rate of loss of water in dry air from ten species of aquatic insects has been measured by Holdgate (78). This has confirmed Shaw's conclusion (77) that the permeability of the cuticle to water is greater than that of terrestrial insects, and that there is no "critical temperature" characteristic of the cuticle of the latter above which the permeability shows a sudden increase.

In some cases the permeability is so low that life is possible in the most unphysiological environments. The larva of *Aedes natronius* has been found in East African Crater Lakes containing up to 0.7*N* sodium carbonate and with a pH greater than 10.5 (79), and that of the fly *Eristalis* will live for 24 hours in concentrated mercuric chloride and indefinitely in a range of acid and alkali between pH 3 and 10 (80). But even *Eristalis*, which has a cuticle impermeable also to oxygen and breathes through a siphon at the water surface, cannot avoid some interchange through the alimentary canal with the constituents of the environment from which it gets its food, and the regulatory mechanisms enabling it to withstand environmental extremes would be worth investigating.

On the other hand there are a number of dipterous larvae which have a portion of the body surface which is not only permeable to water and salts but has a definite function in permitting a limited exchange of these between haemolymph and external medium. Wigglesworth (81) showed that the anal papillae of *Aedes aegypti* are much more permeable than the rest of the body surface and Koch (82) that those of *Culex* and *Chironomus sp.* can absorb chloride from very dilute solutions similar in concentration to that of the water in which they normally live. More recent work by Ramsay (83) has shown that both sodium and potassium are taken up from freshwater by the anal papillae of *A. aegypti*, and this was confirmed with labelled sodium by Treherne (84) who demonstrated that a small proportion of the sodium enters via the gut. This is the main route for absorbtion by some e.g., *Helodes spp.* [Treherne (85)], while others, such as *Sialis*, seem to be unable to absorb from freshwater at all, their supply of inorganic ions being derived from the food. In *Sialis* the dorsal papillae are no more permeable than the rest of the cuticle and the general permeability is in fact so low that it was possible to keep specimens in a healthy condition for more than eight weeks starved and in a stream of glass-distilled water. A physiologically sufficient amount of Na and Cl was retained in the haeomlymph [Beadle & Shaw (86), Shaw (87)]. *A. aegypti* will survive only a few days of such treatment, owing to loss of salt through the papillae [Wigglesworth (81)].

But in addition to the control of exchange through the integument it is necessary to regulate loss through the excretory organs. The malpighian tubules elaborate a fluid from the haemolymph and pass it into the intestine. Before it is finally voided the fluid collects in the rectum which may further alter it by reabsorbtion or excretion. Boné and Koch (88) showed with the trichopterous larva *Limnophilus flavicornis* that the fluid collected by canula near the exit of the tubules contained more or less chloride according to the amount of sodium chloride in the external medium. Shaw (87) found that the urine of *Sialis* can be devoid of Na, K, and Cl due to rectal reabsorbtion and be composed almost exclusively of a solution of ammonium carbonate. Ramsay (83, 89, 90, 91) using his ultramicro-methods for determination of freezing point, Na, and K, showed similar powers for rectal reabsorbtion of Na and K in *A. aegypti* and was able to give a picture of the whole regulatory mechanism in this larva. In freshwater the anal papillae take up Na and K and both are excreted in the fluid from the tubules, which is slightly hypotonic to the blood. The composition of the malpighian fluid and the amount of rectal reabsorbtion are so adjusted as to maintain a remarkable constancy in the concentration of Na and K in the blood in spite of great changes artificially made in the concentration of these in the environment. Thus in freshwater the concentration of Na in the final urine is about half that of the blood and becomes about equal to it when the larva is exposed to 1 per cent NaCl, which is as much as this species can stand. Ramsay was unable to find evidence for separate filtration and reabsorbtion regions of the tubules, and it seems that the excretory system of this and probably other aquatic insects

differ from the vertebrates in the absence of a preliminary filtration. There is a preliminary selective excretion by the malpighian tubules followed by selective absorbtion, and in some cases by selective excretion, in the rectum.

Very few species have been able to colonise natural saline waters [Beadle (6)]. Of those which have been successful only in *Aedes detritus* has the regulatory mechanism been investigated [Beadle (92), Ramsay (89)]. This functions to maintain the haemolymph hypertonic to freshwater and hypotonic to saline water. The anal papillae are much reduced and are as impermeable as the rest of the cuticle, and active uptake of ions from a dilute medium occurs through the gut. It is able to live in highly saline water because it can produce a hypertonic malpighian fluid, which *A. aegypti* cannot, and to concentrate this still further in the rectum. In freshwater the mechanism in both species is apparently the same. Ramsay discovered that the lining of the rectum of *A. detritus* is different from that of *A. aegypti* and contains cells which may be associated with salt excretion as has been suggested for the so called "chloride secreting cells" in the gills of some teleost fish (see section on Fish).

In a closer study of the function of the malpighian tubules of several insects including *A. aegypti* Ramsay (91) found that the concentration of K in the urine is always greater and that of Na usually less than in the haemolymph. Measurement of potential difference across the wall of the tubule indicated that the excretion of potassium is an active process, whereas Na probably passes across by passive diffusion. There is therefore an active circulation of K which the evidence suggests is characteristic of insects. Ramsay (93) with isolated preparations of the tubules of the stick insect *Dixippus morosus* in drops of haemolymph attempted to discover whether this "potassium pump" is the driving force for the passage of water into the tubule which might follow from the osmotic gradient so created. He however, confirmed, what his previous less critical experiments had led him to suspect, that the malpighian fluid is normally somewhat hypotonic to the haemolymph. This suggests that there is a separate active mechanism in the tubules for the excretion of water, but a final conclusion must await on further investigations.

The source of the energy involved in the active transport of ions in insects has been accorded little investigation. But Claus (94) found that the respiratory rate of the brackish water hemipteran *Sigara lugubris*, which is homoiosmotic in an external medium ranging in salinity from 0.5 to 1.8 per cent, is minimal in 0.6 per cent and rises with either dilution or concentration. The osmotic pressure of the haemolymph is normally equivalent to about 0.7 per cent salinity. The same measurements applied to two freshwater species, *Sigara distincta* and *Sigara fossarum*, showed that they are homoiosmotic only in freshwater, in which the respiratory rate is minimal. No definite conclusions can profitably be drawn from these observations in the absence of an estimate of the necessary work to be done in maintaining the observed blood levels.

Hers (95) working with *Chironomus* larvae (*plumosus* group) reported that both the retention of chloride and uptake from dilute solutions after treatment with distilled water were impaired by lack of oxygen. This is rather surprising considering that these larvae normally live in mud where conditions are generally anaerobic. But much more work could profitably be done on animals living in this complicated environment which resembles that of the parasites of the vertebrate alimentary canal in so far as there is a scarcity of oxygen and an abundance of carbon dioxide and dissolved organic substances. Beadle & Beadle (96) found that the larvae of *Sialis* and *Corethra*, both of which normally inhabit the bottom of ponds and lakes, not only survive several days exposure to pure carbon dioxide (devoid of oxygen) but maintain their normal blood chloride and osmotic pressure. The larva of the fly *Gastrophilus intestinalis*, parasitic in the alimentary tract of the horse, is normally exposed to a high tension of carbon dioxide. But it cannot in fact live in a medium devoid of carbon dioxide in which its respiration progressively decreases and the permeability of its haemoglobin-containing cells increases [Levenbook (97)].

It has long been known that the composition of insect blood is peculiar in that chloride is very low, and in fact an inorganic analysis shows a large deficit of undetected anions. Wigglesworth (81) showed with *A. aegypti* larvae that artificial alteration of the chloride in the blood by exposure to distilled water or salt solutions did not produce a corresponding effect on the total osmotic pressure, which led him to conclude that there was a compensatory regulation of the "nonchloride fraction." This phenomenon has since been observed in *A. detritus* [Beadle (92)], in *Sialis* [Beadle & Shaw (86)], in the Dragonfly nymphs *Aeschna* and *Libellula* [Schoffeniels (98)], and in the beetle larva *Helodes* Treherne (85)].

Another peculiarity of the blood is the high concentration of free amino-acids [Florkin (99), Raper & Shaw (100)]. Following the hypothesis that these are in fact the "nonchloride fraction" Beadle & Shaw (86) found that in *Sialis* there is a regulation of the nonprotein nitrogen fraction of the blood which compensates for alterations in chloride in both directions. The total osmotic pressure is thereby maintained in spite of changes in the inorganic constituents. There was some indication that the amino acids are mobilised at the expense of the blood proteins.

Mollusca

Molluscs are primarily marine but the Lamellibranchiata (bivalves) and Gastropoda have colonised freshwater and, in their own way, the Gastropods are one of the most successful groups of land animals. The blood of marine molluscs is generally in equilibrium with seawater. The recent chemical work of Robertson (26, 40) has corrected much of the previous inadequate data and presented a clearer picture of the pattern of ionic regulation in the marine Lamellibranchs, Gastropods, and Cephalopods. In general the above represents the order of increasing powers of regulation of most ions, especially

potassium, which in the blood of the squid *Loligo* is about twice as concentrated as in seawater. Robertson suggests that this high level of K (about 20 m*M*/l) is significantly correlated with the great activity of the Cephalopods. But nerve and muscle activity depends upon a state of electrical polarisation of the cell membrane associated with a high intracellular concentration of K (41). Hayes & Pelluet (42) analysed both muscle and blood in the Octopod *Eledone moschata* and found 101 m*M*/l K in the muscle and 12 m*M*/l in the blood. Steinbach & Spiegelman (43) found 369 m*M*/l K in the giant axon nerve of *Loligo* which bears the same order of relation to Robertson's figure for the blood (20 m*M*/l) as that between the K in nerve fibre and plasma of the Frog (173 and 2.6 m*M*/l) (44). Activity of nerve and muscle is thus dependent, amongst other factors, not upon actual concentration of blood K but upon the relation between this and the concentration in the nerve and muscle cells. In fact Hoyle (45) working with locusts found that increased blood K reduces both the resting muscle cell membrane potential and the tension developed in the leg muscles as well as the jumping activity of the whole animal. Robertson (40) showed from analysis of the contents of the renal sac that the excretory organs play a part in the ionic regulation of Cephalopods.

The Mussel *Mytilus edulis* is a marine Lamellibranch very tolerant of low salinities in estuaries. Previous reports that it had some powers of hypertonic regulation in dilute seawater were not supported by the freezing point measurement of Potts (46) who found blood and water to be isotonic. Even its powers of ionic regulation are not very great, though it maintains somewhat higher concentrations of K, Ca, and total CO_2 than the external water. No other brackish water mollusca seem to have been investigated.

The freshwater bivalve mollusc *Anodonta cygnea* has the lowest blood osmotic pressure recorded for any animal (*ca.* 20 m*M*/l). A hypotonic urine is produced by ultrafiltration from the heart into the pericardial fluid and subsequent reabsorption from the excretory tube (organ of Bojanus) through which the pericardium opens into the mantle cavity (47, 48). Several freshwater bivalves and gastropods have considerable powers of active ion uptake, especially of Na and Cl, which must contribute with the excretory organs to the osmoregulatory mechanism (1). Potts (49) confirmed the low osmotic pressure and determined the ionic composition of the blood of *Anodonta*. He found however that the concentrations of Ca and CO_3 were of the same order as in *Mytilus* and concluded that both are saturated with respect to calcium carbonate in the form of aragonite of which their shells are largely composed. He also determined the rate of urine production in *Anodonta* to be about 1.9 ml./hr. in a 100 gm. animal (50). Hiscock (51) found by freezing point measurements that the blood osmotic pressure of the Australian freshwater Lamellibranch *Hyridella australis* is also low (about 46 m*M*/l) and that the urine is hypotonic. When the blood chloride was raised by immersion in somewhat hypertonic salt solution it was surprising that this was not reflected in a rise in urine chloride.

Pilgrim (52), with the technique used by Wells & Ledingham (32) on rhythmic muscle of Polychaetes, studied the effects of sudden and slow changes of salinity in the perfusion medium on the isolated heart muscle of the three Lamellibranchs: *Mytilus edulis*, *Ostrea edulis*, and *A. cygnea*. In general the same results were obtained. So long as the change was not outside the range of tolerance the effect of sudden alteration of salinity was a complete inhibition of beat followed by recovery after some hours. This inhibition could be avoided if the change was slow. A rather similar result was got with sudden salinity changes on the ciliary beat of the gills of the same three molluscs (53). Pilgrim concluded from the experiments on heart muscle that the tissues are capable of withstanding a greater range of concentration of the medium than would normally be encountered in Nature. The important question which arises from this, as well as from the work of Wells & Ledingham is—what is the immediate cause of inhibition and what happens during the recovery process? It is presumably an upset and a restoration of some ionic relation between cells and medium, the restoration perhaps involving some active process. It should be possible to answer this.

Nematoda

It was for long taken for granted that "roundworms," in view of the comparatively large surface area relative to their size and the apparent absence of excretory organs, must owe their extraordinary ability to withstand unfavourable environments to a thick and impermeable cuticle. Krogh (1) expressed this view but was unaware of the earlier work of Mueller on *Ascaris lumbricoides* (101) and of Schopfer on *Parascaris megalocephala* (102), both large intestinal parasites in the pig and horse respectively. Mueller showed that the cuticle is permeable to several substances including potassium iodide, neutral red, and methylene blue. Schopfer concluded from measurements of freezing point of body fluids and of changes of weight in artificial media that the cuticle is freely permeable to water. Pannikar & Sproston (75) found the same for *Angusticaecum sp.* from the intestine of the tortoise and showed that if kept in a series of seawater dilutions its body fluid osmotic pressure curve was rather similar to that of the crab *C. moenas* in that it was practically isotonic in about 50 per cent seawater and became progressively more hypertonic in greater dilutions.

The free living soil nematode *Rhabditis terrestris* was studied by Stephenson (103). From changes of length in experimental solutions and from observing the behaviour of the alimentary canal he decided that the cuticle is permeable to water and that entrance of water is controlled by the protoplasmic layer under the cuticle and that the alimentary canal plays some active part in osmoregulation.

Hobson *et al.* (104) made a more thorough study of *A. lumbricoides*. Measurement of freezing point showed that the body fluid is normally hypotonic to the intestinal contents of the host. 30 per cent seawater was the best medium for maintaining the worm in the laboratory, and in this the body fluid

is hypertonic. It was also shown to have considerable powers of regulation of Cl, Na, K, Ca, and Mg (105). Water and chloride exchange occurs both through the body wall and through the alimentary canal, which are thus permeable to both. One feature of the regulatory mechanism, which is located in the body wall, seems to be an active excretion of chloride against a concentration gradient so that the chloride of the body fluid is always below that of the medium.

Reference should also be made to the review by Hobson (106) of the general physiology of parasitic Nematodes.

Tunicata

These animals are entirely marine and are interesting in the present connection because, though basically chordate in structure, they possess no excretory organs. Through the branchial chamber and associated structures a very large surface is exposed to the water. The early work on the composition of the blood was reviewed by Krogh (1). The results were unsatisfactory and conflicting. Robertson (40) applied improved methods for collecting and analysing the blood to the two species *Phallusia mammillata* and *Salpa maxima*. There is now no doubt that the blood is practically isotonic with seawater. It contains less than 1 gm./l protein. There is however some ionic regulation in both species resulting especially in a very reduced blood sulphate as compared with seawater. Most of the other ions are regulated to some extent but the two species differ somewhat in detail. The very acid plasma in *Phallusia* (pH 6.6) is associated with a concentration of HCO_3^- ion (i.e., alkali reserve) much lower than in seawater.

Further research on this group may suggest the reasons for failure to colonise freshwaters. It is of possible interest in this connection that the isolated tunicate heart has been found to be relatively insensitive to ionic changes and to hypotonicity of the perfusion fluid (107).

Fish

The Elasmobranch fish have not been investigated since the work of Smith more then twenty years ago (4, 118).

The general pattern of osmotic regulation in Teleost fish has long been known (1, 4, 119). The low blood osmotic pressure in both marine and freshwater forms, as well as anatomical and palaeontological evidence, suggest a freshwater origin. In freshwater species regulation involves active uptake of ions through the gut and gills, with active reabsorption by the kidney tubules and consequent production of hypotonic urine, which compensates for the water absorbed by osmosis through the gills and oral membranes. In marine species the blood osmotic pressure is only a little higher than in freshwater species and is regulated by ingestion of seawater, from which the water, most of the Na, K, and Cl and some of the Mg, Ca, and SO_4 are absorbed from the gut. The Cl, and probably Na and K, are excreted mainly by the gills, the other ions in the urine which is slightly hypertonic. Fresh-

water Teleosts have a hypertonic and marine Teleosts a hypotonic regulation, and those species, such as the eel and salmon, which can pass from one medium to the other, can switch on either mechanism according to need. There is little doubt that the permeability of the integument is very low, due to scales and mucus, and that little exchange with the environment takes place through it (1). Records of marine and brackish species whose passage into freshwater is favoured by a high calcium content of the water is therefore significant (120, 121).

The latest blood analyses were done by Robertson (40) on the powan *Coregonus clupeoides* (freshwater) and the conger *Muraena helena* (marine). The ionic pattern of the blood is very similar in both except that the freshwater fish contains more potassium. He also discusses the state of development of the renal glomeruli in Cyclostomes and fish with reference to the theory of Smith (4) and Marshall (122) that the glomerulus is an adaptation to freshwater life. From a survey of data on this subject and from calculations of Nash (123) on the actual total filtration surface in various Teleosts Robertson decided that evolutionary conclusions based on these data are unwarranted. Filtration depends as much on the hydrostatic pressure in the capillaries as on the filtration surface available, and not significantly on the osmotic gradient. Indeed some aglomerular pipefishes live in freshwater (124).

We await with interest blood analyses of the newly discovered marine Coelocanths *Latimeria* and *Malania*, whose earliest relatives apparently lived in freshwater (171). One question is whether, like Elasmobranchs, they have a blood rendered isotonic with seawater by the retention of urea, or whether, like marine Teleosts, they have a mechanism for hypotonic regulation.

The histochemistry of chloride absorption and excretion by the gills of *Fundulus heteroclitus* has been investigated by Copeland and Pettengill (125, 126, 127). This fish is extremely euryhaline and can live in both fresh and seawater. Eosinophil glandular cells were found on the afferent side of the gill filaments similar to those discovered by Keys and Willmer (128) in the eel and regarded by them as responsible for excretion of chloride in seawater. These cells contain many mitochondria and Golgi bodies whose presence suggests a secretory activity. In fish adapted to seawater there are clear distal vacuoles containing much chloride. In freshwater the vacuoles disappear, but chloride is concentrated in a distal band of cytoplasm. Copeland and Pettengill take this as evidence that the cells perform the two functions of chloride excretion in seawater and chloride absorption in freshwater. This conclusion was further supported by injecting sodium chloride into the gut of freshwater adapted *Fundulus*, which induced the formation of vacuoles in these cells. They are not therefore caused directly by an external rise of salinity, but result from an increase in blood chloride. In seawater-adapted fish phosphatase is concentrated round the distal vacuoles and in freshwater it is densely distributed through the cell. Indirect evidence for Copeland's contention is therefore rather strong, though it implies that the same cell can

rapidly reverse its physiological polarity. It would be interesting to know whether cells having all the appropriate histochemical properties can be found in the gills of other marine and freshwater Teleosts.

In view of the importance of the posterior pituitary in the control of salt and water metabolism in higher vertebrates it is to be expected that the possibility of endocrine control in fish should have been investigated. A recent review is by Fontaine (129). Although the neurohypophysis of Teleosts contains the hormones which produce the "water balance" effect in amphibia and the diuretic effect in all higher vertebrates (see section on Amphibia) no positive results have been got from injecting either mammalian or Teleost extracts into Teleosts (130). Nor has hypophysectomy caused any upset in the regulating mechanism (131, 132, 133). Fontaine suggests that the apparently positive results got by Pickford (134) were probably due to rough handling and points out how difficult it is to experiment with fish in view of the delicacy of the integument and its mucous covering whose permeability is so easily increased by manipulation.

The absence of direct effect of neurohypophysial extracts is however not unexpected because this is also the case with those Amphibia which are completely aquatic (see p. 349). On the other hand histological changes in the neurohypophysis of the salmon in passage from fresh to seawater and vice versa and of marine Teleosts in response to artificial changes in external salinity suggest that the neurohypophysis may have a controlling function acting through some intermediary system [Olivereau (1954), Arvy & Gabe (1954), quoted by Fontaine (129)]. Several authors have produced evidence for the controlling influence of the thyroid in those fish which can live in a wide range of salinity. This has been reviewed by Fontaine (129) and by Smith (135). The evidence is on the whole unsatisfactory and at several points conflicting. Thus Koch & Heuts (136) found evidence for thyroid control of salt regulation in *Gasterosteus*, but Smith's work on the brown trout (135) suggested that the thyroid plays no part in determining salinity tolerance, though a definite effect was produced by injection of doses of thyroxin above the physiological level. He did however induce an increased salinity tolerance by injection of growth hormone prepared from anterior pituitary and in doses which he considered were physiological.

In view of this uncertain link between the endocrine system and the salt and water regulating mechanisms it would seem premature to attempt a synthesis of the factors causing the migration of certain fish between sea and freshwater. But the review of this subject by Fontaine & Koch (113) presents many interesting facts and suggestions.

Cyclostomata

The Cyclostomata are divided on morphological grounds into the Myxinoidea or hagfishes which are purely marine, and the Petromyzontia or lampreys some of which leave the sea to breed in rivers, and a few species are purely freshwater.

Earlier workers found by measurement of freezing point that the blood of the marine myxinoids is slightly hypertonic to seawater (4). Robertson (40) has estimated from analyses of separate inorganic ions, and allowing for protein and urea, that the blood of *Myxine glutinosa* is practically isotonic with seawater. He found however that the inorganic ions are more highly regulated than in the Tunicata.

The only determination to date of the osmotic pressure of the blood of a Petromyzont taken in seawater was made by Burian in 1910 (108). A specimen of *Petromyzon marinus* taken in the Mediterranean (Δ2.30°C.) gave a blood Δ of 0.586°C. Both *P. marinus* and *Petromyzon fluviatilis* when taken from freshwater have a blood osmotic pressure of the same order (Δ0.46–0.54°C.) (109, 110, 111, 112). Burian's single observation was indirectly supported by Morris (112) who found much individual variation in *P. fluviatilis* whilst entering freshwater in ability to withstand return to dilute seawater and to regulate chloride. This he interpreted as evidence of a progressive breakdown of a hypotonic regulating mechanism during the passage into freshwater [see also (113)]. There is therefore little doubt that *P. marinus* and presumably other Petromyzonts resemble marine Teleosts in maintaining a hypotonic blood in seawater.

Wikgren (70) found that *P. fluviatilis* in freshwater is similar to freshwater Teleosts in excreting a very hypotonic urine and in actively absorbing chloride from freshwater. Since the alimentary canal degenerates in the freshwater (breeding) phase, the animal is independent of food for its salt supply. Hardisty (114) compared *P. fluviatilis* with *Petromyzon planeri*, the purely freshwater form. The rate of osmotic inflow of water in freshwater and outflow in dilute seawater is much greater in *P. planeri* than in *P. fluviatilis*. *P. planeri* also has a powerful mechanism for active absorbtion of chloride, and presumably other ions, which enables its ammocoete larva to replace much of the organic constituents of the blood by inorganic salts during its development.

The evolutionary origin of the Cyclostomes is discussed by Robertson (40). Borei's report (115) that the blood of Myxine contains, like the marine Elasmobranchs, a high concentration of urea (3–4 gm./l) led Needham (116) to suggest a freshwater origin for the Myxinoids. But Robertson showed by improved methods that the urea is in fact very low (*ca.* 0.3 gm./l), which is in agreement with Smith (4). He discusses the implications of this and of the glomerular nature of the Cyclostome kidney together with the fragmentary palaeontological evidence, and concludes that the indications are in favour of a marine ancestry. The blood of *Myxine*, though isotonic with seawater, is more highly regulated with respect to ions than that of Tunicates, and the composition of the blood of *Lampetra fluviatilis* from freshwater is very similar to that of a freshwater Teleost fish (40).

Though no work seems to have been done on possible endocrine control of water and salt balance, it should be noted that Lanzing (117) found pitui-

tary extract from *L. fluviatilis* to produce the "water balance" effect when injected into frogs (see section on Amphibia).

Amphibia

The mechanism for salt and water regulation in the Amphibia is of particular interest because they present a gradation from purely aquatic (freshwater) to near terrestrial forms. Their importance in the evolutionary physiology of the Vertebrates is thus obvious. Until recently most of the work has been concerned with frogs, which are truly amphibious and occupy about the middle of this physiological range, but some research has now been done on more extreme types.

The osmotic pressure of the blood is of the same order as that of Teleost fish and of most freshwater invertebrates. Our knowledge of the regulatory mechanisms in frogs was summarised by Krogh in 1939 (1). The skin is highly permeable to water which enters continuously and is passed out in the urine rendered hypotonic through reabsorbtion of salts by the renal tubules. A frog exposed to air of low humidity rapidly loses water through the skin and the blood osmotic pressure rises. A smaller volume of a more concentrated urine is then produced by the kidney which is not in any case able to produce a hypertonic urine. On return to water the original weight is restored and often exceeded by absorbtion of water (137). Krogh (138, 139) was the first to show that frogs actively absorb Na and Cl (but not K or Ca) from freshwater through the skin and that there are two independent mechanisms for these ions. This has been confirmed and analysed in more detail by Jørgensen, Levi & Zeraha (140).

The remarkable properties of the isolated frog skin have been known for many years and it has been used repeatedly for studies of permeability and ion transport. Ussing (141) summarises the aspects of this work which are relevant to this subject and describes his own investigations using radioisotopic Na in an ingenious apparatus whereby he showed that the total current which can be drawn from a short-circuited skin is derived from active inward transport of sodium which is energised by oxidative metabolism. We are reminded of the "sodium pump" which is responsible for the maintenance of the ionic imbalances upon which the activity of the nerve fibre depends (41). In the frog skin it is obviously an important component of the ionic regulatory mechanism. In freshwater fish, as we have already seen, a somewhat similar mechanism must function in the gills, though not in the skin.

In recent years much work has been done on the endocrine control of water and salt balance in Amphibia. This has been reviewed by Heller (137, 142), Jørgensen (143) and Sawyer (144). Much clearer and more significant results have been got than with fish mainly because there is a clear and direct response to injection of posterior pituitary extracts. All of the known sites of water and salt regulation, the skin, kidneys, and bladder, are directly controlled by hormones from the neurohypophysis. The so-called "water

balance" effect, which is peculiar to amphibia, is caused by a hormone present in the oxytocic fraction of the neurohypophyses of all classes of vertebrates. Injection of this causes an increased uptake of water through the skin of the intact frog. It has been shown to act directly on the isolated frog skin causing an increased inward passage of water (145), and also an increased skin current and total sodium flux (146).

As with mammals, injection of neurohypophysial extracts has an antidiuretic effect on the kidney both by reducing glomerular filtration (probably by constriction of the afferent arterioles) and by increasing tubular reabsorbtion of water, with the result that under extreme conditions a minimal volume of urine can be produced almost isotonic with the blood (137, 144, 147).

Ewer (148, 149, 150) found that the toad *Bufo regularis*, when dehydrated, will reabsorb water from the bladder and that this is increased by injection of neurohypophysial extract. This was confirmed by Sawyer (144) for *Rana pipiens*.

There is some evidence that the stimulus to secretion of these hormones by the neurohypophysis is an increase in osmotic pressure, or at least in salt content, of the blood (144). Injection of salt into frogs and toads increases water uptake (151) and reduces the histologically visible secretory material in the gland (152). Levinsky & Sawyer (145) found that the assayable hormone in dehydrated frogs was much reduced.

Evidence for hormonal control of uptake and excretion of salt in intact amphibia is less satisfactory though Jørgensen *et al.* (153) report an increased uptake and excretion of sodium in the axolotl after injection of extract of neurohypophysis, and excretion of chloride in *R. pipiens* is thereby much increased [Sawyer & Sawyer (154)]. Sawyer (144) considers that, though the evidence is scanty, the mechanism for salt regulation is separate from that for water and may also involve the adrenals. The discussion after Sawyer's paper (144), in which Jørgensen describes unpublished experiments demonstrating unimpaired water and salt regulation in *Bufo bufo* after denervation and degeneration of the neurohypophysis, sounds a warning that this subject is by no means ready for facile conclusions.

From a comparative and evolutionary standpoint it is of great interest that both water balance and antidiuretic effects of neurohypophysial extracts are greater the more terrestrial the habits of the species. Thus the two purely aquatic forms, the Urodele *Necturus maculatus* and clawed toad *Xenopus laevis*, show a small water balance response with no antidiuretic effect (at least in *Xenopus*) and *Xenopus*, unlike the frog, is incapable of water uptake after desiccation. Both effects are well marked on all the truly amphibious frogs (*Rana sp.*) which have been tried, but the strongest reactions have been got with toads (*Bufo sp.*) which spend most of their time out of water (150, 154, 155). Howes (156) discovered that the young tadpoles of *Bufo bufo*, which are of course purely aquatic, show no water balance response and that the response increases during larval life and is very large in the adult.

The evidence suggests that neurohypophysial control of water metabolism in vertebrates, for which the skin, kidneys and bladder are the effectors, evolved in parallel with the transition from aquatic to land life. The antidiuretic response is of great importance to purely land vertebrates, but the water balance effect, whereby uptake through the skin is controlled, is peculiar to Amphibia. This is an evolutionary sideline suitable only for life partly in water.

Energetics

It is clear that the regulating mechanisms discussed in this paper require the expenditure of energy. Early observations on changes of respiratory rate apparently associated with changing demands on the osmoregulatory mechanism, as well as on the depressing effects of respiratory inhibitors on osmoregulation were discussed in Krogh's book (1), especially in his chapter on Crustacea. The general conclusion must be that the observed increases in respiratory rate were often much greater than could be accounted for by the extra osmotic work experimentally imposed upon the animal (e.g., *Carcinus*). In some species no increase could be detected (e.g., *Eriocheir*). Schlieper has recently shown (157) that the respiration of isolated gills of the Baltic form of *Mytilus edulis* in a salinity of 15 per 1000 is about 50 per cent more rapid than that of the North Sea form in a salinity of 30 per 1000 and that the rate of the latter is increased by dilution of the seawater. These changes are not associated with changes in the rate of ciliary best. We cannot however get much further with this problem until experiments are devised whereby the extra osmotic work done by an animal or isolated organ can be accurately determined by chemical analysis and can be set against the observed change in respiratory rate. It is obvious that much of the extra respiration recorded in these experiments on whole animals is not connected with osmotic or ionic regulation at the body surface.

There has been some confusion of thought on this subject, but Potts (50) has recently set out clearly what are in principle the mathematical relationships between the minimum osmotic work required and the concentrations of blood, urine, and external medium and the permeability and area of the body surface. He has worked out the consequences of these relationships when applied to the data available for the crustaceans *Potomobius astacus*, *Eriocheir sinensis* and the clam, *Anodonta cygnea*. It follows from these considerations that for an animal in brackish water the production of a hypotonic urine would have very little effect upon the osmotic work required, but the reduction of the blood concentration would bring considerable relief. In freshwater, on the other hand, the production of urine even mildly hypotonic to the blood would greatly reduce the osmotic work and with a urine isotonic with freshwater the work could be reduced by as much as 90 per cent below that needed with a blood-isotonic urine. The absence of a mechanism for hypotonic urine production in brackish water animals (e.g., *Carcinus*) is thus intelligible and a saving is got by some reduction of

blood concentration. The greatest economies are made by freshwater animals by both lowering of blood concentration and production of hypotonic urine.

Beadle & Cragg (6, 66) suggested, mainly from a consideration of higher Crustacea, that adaptation to freshwater evolved in two stages, (*a*) the development in brackish water of a powerful mechanism for absorption of ions which enabled a few animals such as *Eriocheir* and *Potomon*, to live in freshwater whilst retaining a relatively high blood osmotic pressure and without the assistance of the excretory organs, (*b*) lowering of the blood concentration and consequent reduction in the osmotic work required, as well as the production of hypotonic urine; (*b*) is the state of affairs in most freshwater animals. Potts (50) has now pointed out that stage (*a*) (*Eriocheir* and *Potomon*) is in fact accompanied by a sufficient lowering of blood concentration for a considerable saving of energy, and that it is very unlikely that the freshwater bivalves such as *Anodonta*, could ever have passed through stage (*a*) since the very large and permeable gill surface exposed to the medium would make impossibly large energetic demands on an animal with anything but a very low blood concentration, which must therefore have been reduced at an early stage.

It must be remembered that the normal functioning of tissues, especially muscle and nerve, and even their maintenance in a resting condition, involves ionic regulation and expenditure of energy at the cell surface. As Ramsay has pointed out (158) it is the function of certain cells which separate the blood from the external medium to relieve the strain which would otherwise fall directly upon all the cells of the body. But this relief is provided in varying measure in different animals and there must be internal cellular regulating mechanisms awaiting investigation. The tissues of some animals are adaptable to considerable variations in the composition of the blood, others seem to be irrevocably dependent on a very narrow range of conditions.

There is no fundamental difference between active uptake of ions across the general body surface, across a specialised portion of this such as the gills, or across the walls of an excretory tubule which is also a membrane separating the body fluid from the external medium. This last, however, may be regarded as an energy-saving device in that the ionic gradients between blood and tubular ultrafiltrate are much less than those between blood and external medium.

There is little doubt that a reduction in permeability and consequent lessening of the energy required is also characteristic of adaptation to brackish and freshwaters, though this is difficult to measure. A reduction in permeability to water during the course of adaptation to dilute seawater was suggested for *Gunda ulvae* (159) and for *Carcinus moenas* (58). Evidence for the active transport of water independent of ion transport as a component of regulating mechanisms in both tissue cells and whole animals has been presented by Robinson (160). His theory was based mainly upon observa-

tions on mammalian tissues which suggested the presence of a "water pump" countering the inflow of water from the blood into the cells due to the normally hypertonic conditions inside the cells. There is, however, as yet no convincing evidence that active transport of water contributes to the osmoregulation of aquatic animals. That water moves as the result of osmotic gradients set up by active transport of ions is of course obvious.

Genetic Variations in Osmoregulatory Capacity

There are several instances in the older literature of phenotypic variation in resistance to changes or to extremes of salinity artificially induced in an animal by slow acclimitization [(161), p. 484 ff.]. Genotypic varieties are less easy to recognise if the differences in osmoregulatory capacity are unaccompanied by any clear morphological differences. The two species of *Paramoecium* (*aurelia* and *caudatum*) each produced genotypic varieties in respect of resistance to increased salinity (162). The larvae of the mosquito *Anopheles gambiae* var. *gambiae* is found in freshwater and cannot tolerate a salinity much above that of 40 per cent seawater, whereas *A. gambiae* var. *melas* is resistant to as much as 150 per cent seawater (163). Only the eggs are clearly distinguishable and infertile hybrids result from cross breeding (164). An especially interesting case is the European Stickleback *Gasterosteus aculeatus* which has been exhaustively investigated by Heuts (165). There are two main varieties characterised by a different number of lateral plates which is correlated with a difference in the efficiency of the chloride regulating mechanism and other physiological features. Ecological work suggested that these differences are adaptive in relation to the salinity of the natural habitats and intermediates occur as geographically graded series. These observations combined with genetical data got from artificial cross fertilisations enabled Heuts to draw conclusions regarding the evolution and maintenance of these two physiologically distinct groups of populations.

Smith (166) has re-examined the suggestions made by Beadle (167) and Ellis (168) that there are physiological races of *Nereis diversicolor* which differ genetically in their osmoregulatory capacity to suit the salinity range in which they are living, e.g., the North Sea and the Baltic. Smith examined chloride regulation in specimens taken from several marine and estuarine habitats in Britain and from intermediate and low salinities in Denmark and Finland. They were first well acclimatised in the laboratory to a range of salinities. He also analysed the actual salinity regime in these habitats. His experiments provided no evidence of racial differences in capacity to regulate chloride and there is no doubt that the previous suggestions were made on very inadequate grounds. The case for the existence of two physiological races of *Gammarus duebeni* is equally doubtful (see section on Crustacea), and in such cases an answer can be expected only after a combined ecological, physiological, and genetical investigation, such as was done by Heuts on *Gasterosteus*. Some discussion of this subject is also to be found in the review by Prosser (169).

Some General Conclusions

Though no fundamentally new concepts have been introduced during the last fifteen years, some important advances have been made possible by the improvement in micro-techniques. We now have a much more precise picture both of the composition of the body fluids in relation to the external medium and of the location of the processes by which the observed disequilibria are maintained. It has been confirmed that though most marine invertebrates are in osmotic equilibrium with seawater there are none which do not in some degree actively maintain ionic concentration differences across their external surfaces as well as across the walls of their excretory tubules where such exist. Hypertonic regulation by which marine animals have invaded brackish and fresh waters was probably in the first place developed by an intensification of ionic transport aided by a reduction in permeability and a lowering of the internal osmotic pressure. There is no convincing evidence as yet that osmotic gradients between body fluid and external medium are due in any degree to the active transport of water. Complete adaptation to freshwater was got by acceleration of the transport of ions across the walls of the excretory tubules, giving a hypotonic urine, and by a further lowering of the internal osmotic pressure, which is extremely low in animals with unavoidably large permeable surfaces (e.g., Lamellibranch Molluscs).

There are doubtless many factors controlling the rate and efficiency of these mechanisms which have not yet been investigated or even discovered, but during recent years the study of endocrine control, especially in the Amphibia, has advanced considerably.

The power of active transport is one of the major attributes of living matter and basically our problem is one for the cell physiologists (170). In the last few years they have discovered the ionic patterns upon which the functioning of cells, in particular muscle and nerve, depends. This has given us a much clearer idea of what is meant by an efficient regulatory mechanism since we now know more of the conditions which must be maintained at the cell surface for proper functioning of the tissues. A large field of research is thus thrown open into the comparative physiology of osmotic and ionic regulation at the cellular level and directed towards a better understanding of the whole animal in relation to its environment. An intriguing problem is posed by animals having no extra-cellular body fluids, such as Protozoa and Coelenterates. How are those ionic patterns which are presumably necessary for conduction and contraction set up and maintained?

The time is now ripe for investigating the development of regulatory mechanisms during embryonic and larval life. The available ultra-micro methods would surely yield some interesting information.

LITERATURE CITED

1. Krogh, A., *Osmotic Regulation in Aquatic Animals* (Cambridge University Press, London, England, 242 pp. 1939)
2. Schlieper, C., *Biol. Rev. Cambridge Phil. Soc.*, **5**, 309–56 (1930)
3. Schlieper, C., *Biol. Rev. Cambridge Phil. Soc.*, **10**, 334–60 (1935)
4. Smith, H. W., *Quart. Rev. Biol.*, **7**, 1–26 (1932)
5. Pantin, C. F. A., *Biol. Rev. Cambridge Phil. Soc.*, **6**, 459–82 (1931)
6. Beadle, L. C., *Biol. Rev. Cambridge Phil. Soc.*, **18**, 172–83 (1943)
7. Prosser, C. L., Ed., *Comparative Animal Physiology*, Chap. 2, 3 (W. B. Saunders Co., Philadelphia, Pa., 888 pp., 1950)
8. Nagel, H., *Z. vergleich. Physiol.*, **21**, 468–91 (1934)
9. Glick, D., *Techniques of Histo- and Cytochemistry.* (Interscience Publishers, New York, N.Y., 531 pp., 1949).
10. Kirk, P. L., *Quantitative Ultra-microanalysis.* (John Wiley, New York, N. Y., 310 pp., 1950)
11. Shaw, J., *J. Exptl. Biol.*, **32**, 321–29 (1955)
12. Ramsay, J. A., Brown, R. H. J., and Falloon, S. W. H. W., *J. Exptl. Biol.*, **30**, 1–17, 1953
13. Ramsay, J. A., Brown, R. H. J., and Croghan, P. C., *J. Exptl. Biol.*, **32**, 822–29, 1955
14. Ramsay, J. A., *J. Exptl. Biol.*, **26**, 57–64 (1949)
15. Kitching, J. A., *Biol. Rev. Cambridge Phil. Soc.*, **13**, 403–44 (1938)
16. Kitching, J. A., *Symposia Soc. Exptl. Biol.*, **6**, 145–65 (1952)
17. Kitching, J. A., *Symposia Soc. Exptl. Biol.*, **8**, 63–75 (1954)
18. Kitching, J. A., *J. Exptl. Biol.*, **13**, 11–27 (1936)
19. Løvtrup, S., and Pigon, A., *Comptes Rend trav. Lab. Carlsberg.*, **28**, 1–28 (1951)
20. Fowler, C., *Biol. Bull.*, **80**, 265–74 (1941)
21. Hopkins, D. L., *Biol. Bull.*, **90**, 158–76 (1946)
22. Kitching, J. A., *J. Exptl. Biol.*, **31**, 68–75 (1954)
23. Kitching, J. A., *J. Exptl. Biol.*, **31**, 56–67 (1954)
24. Kitching, J. A., *J. Exptl. Biol.*, **31**, 76–83 (1954)
25. Goldacre, R. J., *Intern. Rev. Cytol.*, **1**, 135–64 (1952)
26. Robertson, J. D., *J. Exptl. Biol.*, **26**, 182–200 (1949)
27. Hosoi, K., *Sci. Rep. Tohoku Univ. IV.*, **10**, 377–86 (1953)
28. Palmert, H. W., *Zool. Jahrb. Abt. allg. Zool. Physiol.*, **53**, 212–60 (1933)
29. Lilly, S. J., *J. Exptl. Biol.*, **32**, 423–39 (1955)
30. Jacobs, W., *Z. vergleich. Physiol.*, **24**, 583–601 (1937)
31. Cole, W. H., *J. Gen. Physiol.*, **23**, 575–84 (1940)
32. Wells, G. P., and Ledingham, I. C., *J. Exptl. biol.*, **17**, 337–52 (1940)
33. Fretter, V., *J. Marine Biol. Assoc. United Kingdom*, **34**, 151–60 (1955)
34. Bogucki, M., *Polsk. Arch. Hydrobiol.*, **2**(XV), 237–51 (1954)
35. Bahl, K. N., *Biol. Rev. Cambridge Phil. Soc.*, **22**, 109–47 (1947)
36. Ramsay, J. A., *J. Exptl. Biol.*, **26**, 46–56 (1949)
37. Ramsay, J. A., *J. Exptl. Biol.*, **26**, 65–75 (1949)
38. Peters, H., *Z. Morphol. Ökol. Tiere.*, **30**, 355–81 (1935)
39. Winterstein, H., and Özer, F., *Z. vergleich Physiol.*, **31**, 308–21 (1949)
40. Robertson, J. D., *J. Exptl. Biol.*, **31**, 424–42 (1954)
41. Hodgkin, A. L., *Biol. Rev. Cambridge Phil. Soc.*, **26**, 339–409 (1951)
42. Hayes, F. R., and Pelluet, D., *J. Marine Biol. Assoc. United Kingdom*, **26**, 580–89 (1947)

43. Steinbach, H. B., and Spiegelman, S., *J. Cellular Comp. Physiol.*, **22**, 187 (1943)
44. Fenn, W. O., Cobb, D. M., Hegnauer, A. H., and Marsh, B. S., *Amer. J. Physiol.*, **110**, 74–96 (1934)
45. Hoyle, G., *J. Exptl. Biol.*, **31**, 260–70 (1954)
46. Potts, W. T. W., *J. Exptl. Biol.*, **31**, 376–85 (1954)
47. Picken, L. E. R., *J. Exptl. Biol.*, **14**, 20–34 (1937)
48. Florkin, M., and Duchateau, G., *Physiol. Comparata et Oecol.*, **1**, 29–45 (1948)
49. Potts, W. T. W., *J. Exptl. Biol.*, **31**, 614–17 (1954)
50. Potts, W. T. W., *J. Exptl. Biol.*, **31**, 618–30 (1954)
51. Hiscock, I. D., *Australian J. Marine Freshwater Research*, **4**, 317–39 (1953)
52. Pilgrim, R. L. C., *J. Exptl. Biol.*, **30**, 297–317 (1953)
53. Pilgrim, R. L. C., *J. Exptl. Biol.*, **30**, 318–30 (1953)
54. Jones, L. L., *J. Cellular Comp. Physiol.*, **18**, 79–92 (1941)
55. Robertson, J. D., *J. Exptl. Biol.*, **30**, 277–96 (1953)
56. Robertson, J. D., *J. Exptl. Biol.*, **16**, 387–97 (1939)
57. Shaw, J., *J. Exptl. Biol.*, **32**, 664–80 (1955)
58. Webb, D. A., *Proc. Roy. Soc.* (*London*), **129**, 107–36 (1940)
59. Koch, H. J., and Heuts, M. J., *Ann. soc. roy. zool. Belg.*, **75**, 87–90 (1944)
60. Shaw, J., *J. Exptl. Biol.*, **32**, 383–96 (1955)
61. Ewer, D. W., and Hattingh, I., *Nature*, **169**, 460 (1952)
62. Koch, H. J., *J. Ann. Soc. sci. Bruxelles*, **54**, 346 (1934)
63. Pannikar, N. K., *J. Marine Biol. Assoc. United Kingdom*, **25**, 317–59 (1941)
64. Parry, G., *J. Exptl. Biol.*, **31**, 601 (1954)
65. Parry, G., *J. Exptl. Biol.*, **32**, 408–22 (1955)
66. Beadle, L. C., and Cragg, J. B., *J. Exptl. Biol.*, **17**, 153–63 (1940)
67. Heuts, M. J., *Med. Kon. Vlaams. Acad. Wetensch*, **5**, No. 2, 1–33 (1943)
68. Hynes, H. B. N., *J. Animal Ecol.*, **23**, 38–84 (1954)
69. Beadle, L. C., and Cragg, J. B., *Nature*, **146**, 588 (1940)
70. Wikgren, B. J., *Acta. zool. Fennica*, **71**, 1–102 (1953)
71. Cole, W. H., Helfer, R. G., and Wiermsa, C. A. G., *Physiol. Zoöl.*, **12**, 393–99 (1939)
72. Cole, W. H., *J. Gen. Physiol.*, **25**, 1–6 (1941)
73. McLennan, H., *Z. vergleich. Physiol.*, **37**, 490–95 (1955)
74. Holm-Jensen, I., *Kgl. Dansk Videnskab. Selskab, Biol. Medd.*, **20** (11), 1–64 (1948)
75. Pannikar, N. K., and Sproston, N. G., *Parasitology*, **33**, 214–23 (1941)
76. (Buck, J. B., *Insect Physiology*, Chap. 7 in (Roeder, K. D., Eds., John Wiley & Sons, New York, N. Y., 1100 pp., 1953)
77. Shaw, J., *J. Exptl. Biol.*, **32**, 330–52 (1955)
78. Holdgate, M. W., *J. Exptl. Biol.*, **33**, 107–18 (1956)
79. Beadle, L. C., *J. Linnean Soc. London*, Zool., **38**, 157–211 (1932)
80. Krogh, A., *Ent. Medd.*, **23**, 49–65 (1943)
81. Wigglesworth, V. B., *J. Exptl. Biol.*, **15**, 235–47 (1938)
82. Koch, H. J., *J. Exptl. Biol.*, **15**, 152–60 (1938)
83. Ramsay, J. A., *J. Exptl. Biol.*, **30**, 79–89 (1953)
84. Treherne, J. E., *J. Exptl. Biol.*, **31**, 386–401 (1954)
85. Treherne, J. E., *Trans. R. Ent. Soc. London*, **105**, 117–30 (1954)
86. Beadle, L. C., and Shaw, J., *J. Exptl. Biol.*, **27**, 96–109 (1950)

87. Shaw, J., *J. Exptl. Biol.*, **32**, 353–82 (1955)
88. Boné, G., and Koch, H. J., *Ann. soc. roy. zool. Belg.*, **73**, 73–00 (1942)
89. Ramsay, J. A., *J. Exptl. Biol.*, **27**, 145–57 (1950)
90. Ramsay, J. A., *J. Exptl. Biol.*, **28**, 62–73 (1951)
91. Ramsay, J. A., *J. Exptl. Biol.*, **30**, 358–69 (1953)
92. Beadle, L. C., *J. Exptl. Biol.*, **16**, 346–62 (1939)
93. Ramsay, J. A., *J. Exptl. Biol.*, **31**, 104–13 (1954)
94. Claus, A., *Zool. Jahrb. Abt. Physiol.*, **58**, 365–432 (1937)
95. Heuts, M. J., *Ann. soc. roy. zool. Belg.*, **73**, 173–79 (1943)
96. Beadle, L. C., and Beadle, S. F., *Nature*, **164**, 235 (1949)
97. Levenbook, L., *J. Exptl. Biol.*, **28**, 181–202 (1951)
98. Schoffeniels, E., *Arch. intern. Physiol.*, **58**, 1–4 (1950)
99. Florkin, M., *Mem. l'acad. roy. Belge.*, **16**, 1–69 (1937)
100. Raper, R., and Shaw, J. *Nature*, **162**, 999 (1948)
101. Mueller, J. F., *Z. Zellforsch u microskop. Anat.*, **8**, 361–403 (1928)
102. Schopfer, W. H., *Rev. suisse zool.*, **39**, 59–114 (1932)
103. Stephenson, W., *Parasitology*, **34**, 253–65 (1942)
104. Hobson, A. D., Stephenson, W., and Beadle, L. C., *J. Exptl. Biol.*, **29**, 1–21 (1952)
105. Hobson, A. D., Stephenson, W., and Eden, A., *J. Exptl. Biol.*, **29**, 22–29 (1952)
106. Hobson, A. D., *Parasitology*, **38**, 183–227 (1948)
107. Krijgsman, B. J., *Biol. Rev. Cambridge Phil. Soc.*, **31**, 288–312 (1956)
108. Burian, R., *Pflugers Arch. ges. Physiol.*, **136**, 741–60 (1910)
109. Fontaine, M., *Compt. rend.*, **191**, 680–82 (1930)
110. Fontaine, M., *Compt. rend.*, **191**, 796–98 (1930)
111. Galloway, T. M., *J. Exptl. Biol.*, **10**, 313–16 (1933)
112. Morris, R., *J. Exptl. Biol.*, **33**, 235–48 (1956)
113. Fontaine, M., and Koch, H., *J. Physiologie*, **42**, 287–318 (1950)
114. Hardisty, M. W., *J. Exptl. Biol.*, **33**, 431–47 (1956)
115. Borei, H., *Arkiv. Zool. B.*, **28** (3), 1–5 (1935)
116. Needham, J., *Biol. Revs., Cambridge Phil. Soc.*, **13**, 225–51 (1938)
117. Lanzing, W. J. R., *Acta Endocrinol.*, **16**, 277–84 (1954)
118. Smith, H. W., *Biol. Rev., Cambridge Phil. Soc.*, **11**, 49–82 (1936)
119. Black, V. S., *Publ. Ontario Fish. Research Lab.* (71), 53–89 (1951)
120. Breder, C. M., *Zoologica* **18**, 57–88 (1934)
121. Heuts, M. J., *Natuur. Tijdschr.* (*Belg.*) **26**, 10–14 (1944)
122. Marshall, E. K., *Physiol. Revs.*, **14**, 133–59 (1934)
123. Nash, J., *Am. J. Anat.*, **47**, 425–45 (1931)
124. Grafflin, A. L., *J. Cellular Comp. Physiol.*, **9**, 469–76 (1937)
125. Copeland, D. E., *J. Morphol.*, **82**, 201–28 (1948)
126. Copeland, D. E., *J. Morphol.*, **87**, 369–80 (1950)
127. Pettengill, O., and Copeland, D. E., *J. Exptl. Zool.*, **108**, 235–41 (1948)
128. Keys, A. B., and Willmer, E. N., *J. Physiol.*, **76**, 368–78 (1932)
129. Fontaine, M., *Mem. Soc. Endocrinol*, (5) 69–82 (1956)
130. Fontaine, M., and Raffy, A., *Compt. rend. soc. biol.* **144**, 6 (1950)
131. Fontaine, M., Callamand, O., and Olivereau, M., *Compt. rend.*, **228**, 513 (1949)
132. Callamand, O., Fontaine, M., Olivereau, M., and Raffy, A., *Bull. inst. oceanog.* (984) 1–6 (1951)
133. Matthews, S. A., *Biol. Bull.* **64**, 315–20 (1933)

134. Pickford, G. E., *Anat. Record.*, **115**, 409 (1953)
135. Smith, D. W., *Mem. Soc., Endocrinol.* (5), 83–101 (1956)
136. Koch, H. J., and Heuts, M. J., *Arch. Intern. Physiol.*, **53**, 253–66 (1943)
137. Heller, H., *Experientia.* **6**, 368–76 (1950)
138. Krogh, A., *Skand. Arch. Physiol.* **76**, 60–73 (1937)
139. Krogh, A., *Z. vergleich Physiol.* **25**, 335–50 (1938)
140. Jørgensen, C. B., Levi, H., and Zerahn, K., *Acta. Physiol. Scand.*, **30**, 178–90 (1954).
141. Ussing, H. H., *Symposia Soc. Exptl. Biol.*, **8**, 407–22 (1954)
142. Heller, H., *Biol. Rev. Cambridge Phil. Soc.*, **20**, 147–58 (1945)
143. Jørgensen, C. B., *Acta Physiol. Scand.*, **22**, Suppl. 78, 1–79 (1950)
144. Sawyer, W. H., *Mem. Soc. Endocrinol.* (5), 44–45 (1956)
145. Levinsky, N. G., and Sawyer, W. H., *Proc. Soc. Exptl. Biol. Med.*, **82**, 272–74 (1953)
146. Fuhrman, F. A., and Ussing, H. H., *J. Cellular Comp. Physiol.*, **38**, 109–30 (1951)
147. Jancso, N., *Speicherung. Stoffanreicherung im Retikuloendothel* 267–75 (1955)
148. Ewer, R. F., *J. Exptl. Biol.*, **27**, 40–49 (1950)
149. Ewer, R. F., *J. Exptl. Biol.*, **28**, 374–84 (1951)
150. Ewer, R. F., *J. Exptl. Biol.*, **29**, 429–39 (1952)
151. Jørgensen, C. B., *Acta Physiol. Scand.* Suppl. 53 (1948)
152. Hild, W., *Virchow Arch., Pathol. Anat. Physiol.*, **319**, 526– (1952)
153. Jørgensen, C. B., Levi, H., and Ussing, H. H., *Acta Physiol. Scand.*, **12**, 350– (1946)
154. Sawyer, W. H., and Sawyer, M. K., *Physiol. Zool.*, **25**, 84– (1952)
155. Steggerda, F. R., *Proc. Soc. Exptl. Biol. Med.*, **36**, 103–6 (1937)
156. Howes, N. H., *J. Exptl. Biol.*, **17**, 128–38 (1940)
157. Schlieper, C., *Kiel. Meeresforsch.* **11**, 22–33 (1955)
158. Ramsay, J. A., *Symposia Soc. Exptl. Biol.* **8**, 1–15 (1954)
159. Beadle, L. C. *J. Exptl. Biol.*, **11**, 382–96 (1934)
160. Robinson, J. R., *Symposia Soc. Exptl. Biol.*, **8**, 42–62 (1954)
161. Heilbrun, L. V., *An Outline of General Physiology* (W. B. Saunders Co., Philadelphia, Pa, 000 pp., 1943)
162. Gause, G. F., *Quart. Rev. Biol.*, **17**, 99–114 (1942)
163. Ribbands, C. R., *Ann. Trop. Med. Parasitol.* **38**, 85–000 (1944)
164. Muirhead-Thomson, R. C., *Mosquito Behaviour.* (Edward Arnold Co., London, England, 000 pps. 1951)
165. Heuts, M. J., *Evolution*, **1**, 89–102 (1947)
166. Smith, R. I., *Biol. Bull.*, **109**, 453–74 (1955)
167. Beadle, L. C., *J. Exptl. Biol.*, **14**, 56–70 (1947)
168. Ellis, W. G., *J. J. Exptl. Biol.*, **14**, 340–50 (1937)
169. Prosser, C. L., *Biol. Rev. Cambridge Phil. Soc.*, **30**, 229–62 (1955)
170. Krogh, A., *Proc. Roy. Soc.* (*London*), B, **133**, 140–200 (1946)
171. Romer, A. S., *Vertebrate Paleontology*, p. 121 (University of Chicago Press, Chicago, Ill. 1947)

HEART[1,2]

By M. B. Visscher and G. J. Stephens
Department of Physiology, University of Minnesota, Minneapolis

The Invertebrate Heart

Pacemaker activity.—An important series of investigations aimed at exploration of neural activity in the cardiac ganglion (pacemaker) of the crustaceans has been undertaken by Maynard (1, 2). In the normally beating lobster heart a series of discharges from several ganglion cells precedes and accompanies the early part of the mechanical response. Characteristics of the response of the ganglion units to electrical stimulation were described by Maynard (3). The spontaneous rate of firing of isolated large neurons is greater than that of the synchronized burst and the author suggests that there is a reciprocal interaction among ganglion units such that a period of synaptic hyperexcitability alternates with a postexcitatory depression. The large cells are considered the motor neurons since the muscle twitch and action potential are associated only with the activity of these cells; the small neurons may be removed without preventing the beat, provided the area remains innervated with fibers from the large cells.

Hagiwara & Bullock (4) studied intracellular potentials in the cells of the cardiac ganglion and found that resting potentials are about 60 Mv. Patterned bursts of large cell activity synchronized with the other cells begin with a 20 mv. depolarization on the falling phase of which smaller slow deflections are superimposed. From their data the conclusions were drawn that each of the large cells appears to be innervated by one presynaptic fiber which probably arises from one of a group of small cells which normally, therefore, act as pacemaker elements.

Krijgsman *et al.* (5) found that rotenone depresses, and tetraethylpyrophosphate greatly enhances, heart activity in the cockroach *Periplaneta.* Krijgsman & Krijgsman-Berger (6), in studies on the pharmacology of the

[1] In this review the papers published in the years 1951–1955 inclusive on the invertebrate heart have been covered because earlier reviews in this series have not dealt systematically with this field, which we consider to be important from the standpoint of elucidation of basic mechanisms. With respect to vertebrate cardiology the literature coverage is limited to the calendar year 1955, except for a few papers not cited earlier or particularly relevant to points of emphasis. The authors regret the necessity, because of space limitations, of eliminating reference to numerous papers with considerable interest to applied cardiology but with less fundamental physiological importance. The clinical investigator is referred to the *Annual Review of Medicine* for this coverage.

[2] The following abbreviations have been used in this chapter: ATP (adenosinetriphosphate); CP (creatinephosphate); BAL (2,3-dimercaptopropanol); ADP (adenosinediphosphate); AMP (adenosinemonophosphate); ECG (electrocardiograph); BCG (ballistocardiogram).

heart of the same species, adduced evidence for assuming that in this animal there is a neurogenic pacemaker with adrenergic properties controlled by a cholinergic accelerator nerve.

Bellemare & Belcourt (7) studied the effect of a cyanide analogue of DDT on the same species (*Periplaneta*) and observed heart pulsations long after general paralysis had occurred, causing these authors to question Krijgsman's conclusions as to the neurogenicity of the cockroach pacemaker. It seems clear from other work, however, that many neurogenic hearts possess independent automaticity which becomes evident when the overriding neural stimuli are obliterated. The heart function of *Daphnia* (water flea) was studied by Bekker & Krijgsman (8) with pharmacologic agents, including acetylcholine, tetraethylpyrophosphate, pilocarpine, epinephrine, digitalen, and rotenone. The authors concluded that their results accord with the assumption of a myogenic pacemaker inhibited by extracardiac cholinergic nerves, unlike the case in many arthropods. Ripplinger (9), using topical application of acetylcholine on various areas of the ventricle of the snail *Helix*, concluded that the rhythmic "driving system" is at the tip of the ventricle despite the fact that systolic contractions are initiated at its base; this implies a myocardial conduction system. Euler *et al.* (10) studied the pharmacology of the heart of another mollusc, the gastropod *Aplysia*, and confirmed earlier findings that the inhibitory effect of acetylcholine in low concentrations was not blocked by atropine. It is of interest to note that in this animal no spontaneous activity was present in a heart freed from adjacent ganglia. Divaris & Krijgsman (11) in a careful series of experiments studied heart physiology in the pulmonate snail *Cochlitoma*. From experiments with ligatures applied to various portions of the heart, local warming and cooling, and especially variously placed cauterizations, the authors concluded that normal cardiac activity in this snail is explainable in terms of a "generalized pacemaker" subject to inhibition from an area in the auricle and stimulation from a region in the aortic junction. Histological studies did not reveal nervous elements in either of the regulatory centers; which fact, however, need not imply their absence. The question as to whether the two branches of the visceral nerve which supply the heart influence its activity via the two regulatory areas previously described remains to be elucidated.

Prosser & Judson (12) investigated the pharmacology of the spontaneously beating haemal vessel of the echinoderm *Stichopus*. Based on a tentative analogy with other hearts, the beat would appear to be myogenic in origin; the action potential is a simple wave of negativity. The physiology of a scorpion heart was investigated by Kanungo (13). Central nervous stimulation and direct stimulation of the heart were without effect on heart rate and amplitude. The author concluded that on the basis of the Needham classification the pacemaker is of myogenic nature.

Neural control.—Alexandrowicz (14, 15, 16), in a series of papers describing anatomical investigations of several crustaceans offered further evidence that in this group the heart innervation follows a basic pattern of three sys-

tems of nerve elements. In addition, the same author (17) described nerve trunks of unusual character (pericardial organs) lying in the pericardial cavity, while Alexandrowicz & Carlisle (18) tested the hypothesis that they serve a neurosecretory function by adding extracts of these structures to the fluid perfusing isolated hearts of several crustaceans. In *Cancer*, *Homarus* and *Squilla* the extracts produced a positive chronotropic and inotropic effect, similar to that of epinephrine and norepinephrine on the hearts of these animals, and in *Maia* had a positive inotropic and negative chronotropic effect. The *Cancer* extracts gave the fluorescence reaction characteristic of epinephrine and related compounds. In the spiny lobster *Panulirus* Maynard (1), by electrical stimulation, found two pairs of cardioaccelerator and one one pair of cardioinhibitory nerves arising in the anterior portion of the thoracic ganglion, fibers from which join to form the dorsal nerve making connections with the cardiac ganglion. In *Homarus* (2) the conduction-velocity of the inhibitor fiber was shown to be greater than that of the accelerator.

Needham (19) performed a series of experiments elucidating the physiology of the heart of the isopod *Asellus*. Acetylcholine accelerates in high concentration and epinephrine is without effect. He demonstrated an accelerator nerve and showed that transection of the ventral nerve cord slows the heart *in situ*. Excluding NaCl from the bathing medium produced complete asynchrony. Tension was shown to be a significant regulatory factor in heart activity. Ripplinger (20, 21) and Jullien & Ripplinger (22) studied the heart of the edible snail *Helix* confirming and extending earlier descriptions of a dual extrinsic innervation corresponding functionally to the vertebrate vagal and sympathetic control. The relations betwen these and the heart are different during activity and hibernation, which the authors attribute in part to an ionic alteration during the latter physiologic state. Jullien *et al.* (23, 24) isolated an acetylcholine-like material (leech-muscle assay) from denervated hearts but concluded that it does not function as a chemical mediator in cardiac activity. In the course of faradization of the visceral nerve, Ripplinger & Mercier (25) and Jullien *et al.* (26) found a "vagal substance" liberated which is ambivalent in its action depending on the concentrations used; acetylcholine and acetylcholine-esterase gradients in the tissues of the heart were also investigated. A stimulating action on the isolated *Helix* heart of media bathing the lung, hepatopancreas and various other tissues, as well as ventricular perfusates following visceral nerve stimulation, was shown [Jullien *et al.* (27, 28)].

From an investigation of the mechanism of the depressant action of acetylcholine on the heart of the clam *Venus*, Welsh & Taub (29) concluded that a carbonyl group at a maximum distance of 7 Å from a quaternary nitrogen is an important linking group for the receptor protein of the heart of this form. From studies on the relationship between electrical stimulation and acetylcholine inhibition on the heart of the same animal, Welsh & Slocombe (30) concluded that the acetylcholine system is intimately associated with the electrical aspects of excitation. Mytolon (benzoquinonium)

and related compounds were studied with respect to their acetylcholine anatagonism on the heart of *Venus* by Luduena & Brown (31).

Zacks & Welsh (32) adduced evidence that the physostigmine potentiation of acetylcholine action is due to inhibition of serum cholinesterase in the heart muscle. Welsh & Taub (33) demonstrated the ineffectiveness of pentamethonium as an acetylcholine antagonist on the *Venus* heart, and the powerful acetylcholine-blocking effect of Mytolon. Ten Cate & Reesinck (34) found a negative inotropic and positive chronotropic effect of acetylcholine on the ventricle of the fresh-water mussel *Anodonta*, with physostigmine potentiating this effect. They concluded that the heart is cholinergically innervated. Pilgrim (35), from experiments in which histamine was applied to isolated ventricle strip preparations of two lamellibranch molluscs, concluded that the drug probably does not function as a natural moderator of cardiac activity in these animals. The same author (36), studying the action of various concentrations of acetylcholine on the hearts of a group of lamellibranchs found that the responses fall in a graded series from inhibition and diastolic arrest to increased activity and contracture, depending on animal species and drug concentration, and postulates that the differences are based on the degree to which pacemaker, muscle fibers or both are affected.

Florey (37) adduced evidence for nervous control of the tubular beat-reversing heart of the tunicate *Ciona*. He found that when the intact heart is exposed to strychnine (1:6000) the advisceral and then the abvisceral centers of automaticity become paralyzed; if the ganglion is then extirpated, the two centers resume activity and the heartbeat approaches the normal.

The reactions of the heart of the squid *Eledone* to various drugs were studied by Fänge & Östlund (38) and Östlund (39) who found that epinephrine and norepinephrine produce a strong positive inotropic and a moderate positive chronotropic effect.

Based on a series of experiments testing the rate and amplitude sensitivity of the heart of various molluscs to enteramine, Erspamer & Ghiretti (40) suggested that this compound many possibly be the normal cardioaccelerator substance in these animals. Bacq *et al.* (41) demonstrated the identity of serotonin, enteramine and 5-hydroxytryptamine and gave convincing evidence for the hormonal role of 5-hydroxytryptamine in *Octopus vulgaris*.

Welsh (42) studied possible mechanisms normally responsible for excitation of the *Venus* heart and found that 5-hydroxytryptamine has a powerful stimulating action when applied in very low concentrations ($10^{-10}M$). This compound produces a response similar to that induced by stimulation of regulatory nerves to the heart under certain conditions (i.e., blockage of acetylcholine inhibition by Mytolon). He also found that certain of the ergot alkaloids excite the heart.

Florey & Florey (43) found a substance in nervous tissues of a group of crabs as well as in the ganglia of the squid *Sepia* which, on the basis of chemical studies and biological activities can be identified as 5-hydroxytryptamine. Extracts of these tissues have a powerful positive ino- and tonotropic effect

on the hearts of both squid and crab. The results of a detailed series of experiments led them to postulate that this compound is probably the transmission substance of the accelerator heart nerve in most cephalopods and may be identical with the compound produced by the pericardial organs of the decapod crabs. [See Alexandrowicz & Carlisle (18).] Welsh (44) reviewed evidence supporting the view that 5-hydroxytryptamine is the cardiac excitatory neurohumor in *Venus*. The same author (45) suggested several marine invertebrate animals, the heart of which are useful for the bioassay of acetylcholine and 5-hydroxytryptamine. Because of the sensitivity of the heart of the freshwater mussel *Anodonta* to 5-hydroxytryptamine, Fänge (46) suggests its use for bioassay of this compound.

Mechanical activity and morphology.—The morphology and physiology of the tubular heart of an anopheles mosquito in the larval, pupal and adult stages were studied by Jones (47). Careful dissection revealed no extrinsic innervation of the heart in any developmental stage, while ether anesthesia produced cessation of activity in all larval organs except the heart, in which only moderate slowing of rate occurred. Jones interprets these results as indicating the myogenic nature of the pacemaker. The effects of β-methylcholine pilocarpine, epinephrine, atropine, and strychnine on the adult heart were tested and in no case did acceleration occur, thus demonstrating an apparent basic difference from the well-innervated neurogenic hearts of many other insects. Blocking of all thoracic and abdominal spiracles lowers the heart rate precipitously and mechanical prevention of abdominal respiratory movements caused arrest of the heart even with all spiracles open. As the author points out, the factors responsible for the regulation of heart activity in this form require further study.

Various hypotheses have been adduced to account for the phenomenon of periodic change in the direction of heart beat, with a resultant reversal of blood flow, as seen most strikingly in the tunicates, with the "back-pressure" school of thought generally predominating. Haywood & Moon (48) reported experiments which show that as the rate of the heart beat increases in the temperature range of 4 to 30° C the reversals take place more frequently. The mechanism of the beat reversal, which must imply a shifting pacemaker, was not explored; if pacemaker activity rests on fundamental metabolic processes then interpretations other than those of the authors may be made from the temperature experiments. Millar (49) has observed reversal of beat in opened, as well as isolated, hearts of another species of tunicate and states that the back-pressure theory is untenable. He concluded from his work that there is an inherent pattern of reversal in the heart of this form, but does not deny the influence of pressure factors in the intact animal.

A detailed study of the physiology of the lepidopteran heart was performed on the moth *Telea* by Tenney (50). Various types of heart reversal occur in the normal animal and even in the isolated preparation and these patterns are described and classified. The author studied conduction time, excitability, and action potentials in the various segments of the heart. The

heart muscle is striated with anastomoses and the beat is probably myogenic but under the influence of regulatory nerves. Burger & Smythe (51), from studies on the lobster *Homarus*, concluded that in the intact animal the circulation is primarily heart-driven. Intraventricular blood pressure measurements were made by means of a strain-gauge and string galvanometer; diastolic aortic pressures tended to vary directly with heart rate. Nutting (52) made a survey of the heart and associated structures of 91 species of orthopteroid insects, using detailed dissections and vital staining on live heart preparations and histological studies. The incurrent system is ostial. In addition, the author made use of his structural findings in the elucidation of evolutionary relationships among these groups of insects. Silén (53), studying the circulatory system of a group of isopods (pillbugs), found that the heart/body volume ratio is much greater in terrestrial than aquatic forms. He described in detail the course of the circulation and the anatomy of the system, discussing its evolution paralleling the transition from aquatic to terrestrial habitat. Jullien & co-workers (54), investigating factors influencing rate and rhythm of the heart in the edible snail *Helix*, found that sufficient insufflation of the lung decompresses the heart after which, deprived of hemolymph, it can function for several hours but with marked disturbances of rhythm. They (55) also measured pulmonary vein pressure which fluctuated with respiration, an increase in pulmonary vein pressure being associated with an increase in heart rate. High oxygen content tends to depress the heart rate.

Miscellaneous observations.—Ventricle strip preparations from species of marine, estuarine, and fresh water molluscs were used by Pilgrim (56) for studies of heart reactions to osmotic changes. Cardiac and respiratory rhythms in the amphipod *Gammarus*, as influenced by temperature, cyanide and azide, were studied by Potter (57). Binet *et al.* (58) and Jullien *et al.* (59) found that, when added to the bathing medium, phenylalanine, adenosine, and especially glucosamine increase the survival time of isolated *Helix* hearts. Corda (60) compared acetylcholine and direct electrical stimulation effects on smooth muscle of the *Helix* ventricle and the striated ventricular myocardium of vertebrates. A comparison of the cardiac effects of chlorinated hydrocarbon and dinitro- insecticides was made by Orser & Brown (61). Beard (62) reviewed the cardiac physiology of insects. Krijgsman (63) and Krijgsman & Divaris (64) presented comprehensive reviews of contractile and pacemaker mechanisms in the arthropods and the molluscs, respectively.

Mammalian and Lower Vertebrate Cardiology

Physiological chemistry of heart muscle.—Harvey (65) found, as he says, "quite unexpectedly" that creatinephosphate (CP) incorporated P^{32} at a rate more than twice that of ATP in the guinea pig heart. Perhaps equally significant is the fact that the inorganic phosphate fraction (obtained by 0.3

N perchloric acid extraction) also equilibrated with plasma P^{32} much more slowly than did the CP. This might indicate either the existence of nonmixing intracellular pools of inorganic phosphate, or an artefact due to splitting of bound phosphate during extraction. Digitoxin (0.12 mg per kg) lowered the rates of incorporation of P^{32} into ATP, CP and ester phosphate, as well as with the inorganic phosphate fraction of heart muscle. Janke (66) reported further studies on ATP metabolism in relation to contracture-producing agents and extended the range of conditions under which contraction fails to induce ATP breakdown.

Garb *et al.* (67) studied the effects of glutathione and its components upon the excitability and contractility of cardiac muscle. Using papillary muscle from cat heart they found that either cysteine or reduced glutathione lowered the threshold of excitability, but that only cysteine altered tension production. Methionine on the other hand did not influence irritability but augmented tension. BAL, a compound with free sulfhydryl groups, was found to diminish excitability without significant effects on tension production. Therefore the actions are not wholly nonspecific for sulfhydryl groups. They noted empirically that a cupric salt greatly increased the tension production of the ventricular papillary strip when added in 8×10^{-4} *M* concentration, with a reversal of the effect at 1×10^{-2} *M*. The role of monoiodoacetate in the poisoning of muscle was reinvestigated by Fleckenstein *et al.* (68), who found that in muscles so poisoned there was, after most of the measurable creatine phosphate was gone, a significant amount of work performed without further CP breakdown or ATP hydrolysis. The existence of thiol groups essential to heart muscle lactic dehydrogenase activity was demonstrated by Neilands (69), using *p*-choromercuribenzoate as the sulfhydryl binding reagent.

Benson *et al.* (70) and Benson (71) studied the reproducibility of methods for quantitation of the actomyosin content of dog ventricular muscle. They found that in myocardium from dogs in chronic heart failure induced by surgical valve lesions the extracted actomyosin solutions had lower viscosities per unit of ATPase activity than in the normal, and that the changes in viscosity in response to addition of ATP were less.

Studies on glycerol-extracted heart muscle have been reported. Hawkins & Smith (72) described methods useful with the frog heart. Glycerol extracted myocardial fibers require about fives times as high an adenosine triphosphate concentration to induce maximum tension development as does comparably treated skeletal muscle, according to Ranney (73). On the other hand, the concentration optimum of Mg^{++} is similar for the two types of extracted fibers and the two both show spontaneous relaxation after ATP-induced tension development. Uridine triphosphate has effects similar to ATP in the myocardial fiber preparation.

Stutz *et al.* (74) were unable to find an effect of lanatoside C upon the resting tension or the tension changes upon addition of ATP to extracted strips

of dog heart muscle, in contrast to the positive effects described by Robb & Mallov (75) on actomyosin threads. The difference in result is as yet unexplained.

An interesting and probably important difference in the finer structure of cardiac and skeletal muscle in vertebrates was studied by Kisch (76). He noted that there are proportionately 500 times as many mitochondrial structures of the sarcosome type in cardiac as in skeletal muscle of the rat and guinea pig. He (77) studied the same structures in the human heart from autopsy material where ovoid "ghosts" of similar shape appear in abundance. The fact that the flight muscles of the hornet and the bumble bee [Kisch (78) and Kisch & Philpott (79)] also possess sarcosomes in large number was suggested by the authors to indicate a probable function for these structures related to their high contraction frequency and presumed high recovery rate.

Holton (80) made studies by spectrophotometric methods of the cytochrome system of rat heart sarcosomes. The results indicate that the kinetics of extinction changes are strongly affected by the presence of 2:4-dinitrophenol and by ADP, confirming earlier suggestions that cytochrome b reduction is coupled with oxidative phosphorylation. Lemberg *et al.* (81) described methods for the estimation of cytochromes a and a_3 in heart muscle. Studies of oxidative phosphorylation by heart muscle sarcosomes were reported by Slater (82), with α-ketoglutaric acid as hydrogen donor and added ferricytochrome c as acceptor. The reaction was found to be sensitive to 2:4-dinitrophenol, indicating the involvement of respiratory chain phosphorylation.

Lorber & Cook (83) studied in perfused heart muscle and in slices the metabolism of sodium butyrate-3-C^{14}. Their results were interpreted to be in harmony with reaction sequences postulated by Mahler (84). The acetate-activating enzyme activity of heart muscle was investigated by Hele (85), who partially purified by electrophoresis a protein constituent which catalyzes the reaction of ATP with coenzyme A and acetate to acetyl coenzyme A and AMP and inorganic pyrophosphate. Cooper (86), in studying succinic dehydrogenase activity in the prenatal and postnatal rat heart, found that the ventricle atrium succinic dehydrogenase concentration ratio increases with the age of the animal. He postulated that the correlation between the intracellular localization of the enzyme in various chambers at different ages may possibly be associated with mitochondrial number and function.

The glycogen and acid-labile phosphate contents of fibrillating left ventricular muscle in the dog remained nearly normal so long as perfusion with oxygenated blood was maintained, according to Paul *et al.* (87). The values fell rather slowly when perfusion was stopped. Glycogen synthesis in heart muscle homogenates was studied by Meyer *et al.* (88), who found no evidence of synthesis in material from dog myocardium, but considerable increase in the trichloracetic acid soluble fraction in rat heart homogenate when well oxygenated and at high (5.4 per cent) glucose concentration. No synthesis occurred at low oxygen tension (20 mm. Hg.) and none at high oxygen levels

when the glucose level was at 1 per cent. Russell & Bloom (89) reported on the trichloracetic acid-soluble fraction of glycogen in heart muscle. Bloom & Russell (90) reported that administration of epinephrine or norepinephrine (0.3 mg./kg.) causes the heart of the rat to gain trichloracetic acid-soluble glycogen after four hours.

A contribution was made to the metabolic characteristics of tissue grossly identified as the atrioventricular bundle (of His) from bovine hearts by Murray (91). It was found that the oxygen consumption of conducting bundle tissue slices measured by manometric methods was about a fifth that of ventricular muscle. The difference in connective tissue content could not account for the metabolic rate discrepancy. The inference drawn was that the bundle tissue is chemically differentiated from contractile myocardium.

Östlund (39) studied the catecholamine content of the hearts of various lower vertebrates and extended his investigations on the cardiac influence of epinephrine and norepinephrine in these forms. Raab & Gigee (92) reported studies on catechols in heart and skeletal muscle. They (93) also reported increases in epinephrine content of heart muscle in patients dying of heart failure as compared with normal hearts. Conditions for extraction and identification of heart muscle protein were studied by Sobel *et al.* (94). Johnson & Leone (95) applied serological techniques to the study of embryological development of proteins found in the heart of the adult chicken.

Ungar *et al.* (96) studied arterial-coronary sinus differences in concentration of glucose and other substances in patients with diabetes mellitus and in dogs after alloxan. They found extremely great variability in glucose extraction from the coronary blood, ranging in normal humans from 0.9 to 15.0 mg. per cent, and in the diabetic from 0.06 to 5.7 mg. per cent. Calculations of myocardial utilization rates yielded a similarly large spread of values. Comparable data were obtained for pyruvate, lactate, amino acids, ketones, and fatty acids. Only for the fatty acids was there a very clear-cut difference, in the direction of an increased utilization in diabetes. Statistical treatment of the data showed that lactate utilization was greater in the normal than in the diabetic ($P < 0.05$). The quantity calculated for utilization includes both metabolism and storage. When compared with the simultaneously estimated cardiac oxygen consumption the amounts of material disappearing from the blood would, if oxidized, require from 80 to 650 per cent of the oxygen used. Obviously if the heart oxygen consumption figures and the material utilization figures are both correct, there must have been burning of endogenous fuel in a few cases and large storage in others. Thus although the authors have supplied much interesting factual data it is probably unjustified to deduce the nature of the metabolic mixture from them.

Lüllmann (97) published an extensive review of the effects of caffeine and theophylline on the metabolism of heart muscle. Bing (98) summarized existing data on myocardial metabolism and chemistry from coronary sinus catheterization studies in man and other species and also dealt with reports on

the metabolism of the isolated heart. Von Korff (99) reviewed the information concerning solubilized enzymes from heart muscle, from cell particulates, and from myocardial slice preparations.

Excitation, conduction and electrophysiology.—The actions of acetylcholine in relation to myocardial contraction were the subject of a number of important papers. Burn & Walker (100) reported that such anticholinesterases as physostigmine, neostigmine, and diisopropylfluorophosphonate cause a slowing of the heart rate in the isolated, denervated heart-lung preparation of the dog. Only the inhibitors of pseudocholinesterase are active, however. A specific inhibitor of true cholinesterase, 284.C.51, was found to be inactive. Atropine abolishes the anticholinesterase effects. Burn *et al.* (101) studied the phenomenon of heart block in the electrically driven heart in the heart-lung preparation. Physostigmine or neostigmine lowers the rate at which atrioventricular block occurs and atropine restores the situation to normal. Since physostigmine leads to acetylcholine accumulation, it appears that the latter may be responsible for the block under these circumstances. Atrial fibrillation is induced at rapid rates of stimulation in hearts treated with pseudocholinesterase inhibitors. The same authors (102) showed that continuous intravenous infusions of acetylcholine in the dog heart-lung make the atria susceptible to fibrillation upon rapid stimulation. The fibrillation persists after cessation of stimulation so long as the drug infusion continues. When it is stopped or reduced in amount, flutter occurs and later a normal rhythm appears. The interesting related observation was made by Glaesser & Tedeschi (103) that the maximum rate of stimulation which the isolated rabbit atria will follow is increased by physostigmine, neostigmine, and diisopropylfluorophosphonate in concentrations to 10^{-6} g/ml. The concept of Burn (104) that acetylcholine has complex effects on the myocardium which are not readily explained in terms of inhibition was discussed by Spadolini (105). Rothschuh (106) and Rothschuh & Berkel (107) investigated the total acetylcholine content of heart muscle and found it to be increased after treatment with esterase inhibitor, more consistently in atrial than in ventricular muscle. Westermann (108) and Holtz & Westermann (109) studied isolated atria of the dog, rat and guinea pig in relation to natural and synthetic choline esters, finding that proprionyl and butyryl cholines had a nicotine-type effect.

Fänge & Östlund (38), in comparing certain aspects of the pharmacology of teleost and elasmobranch fishes, found that the heart of *Myxine*, a cyclostome, was indifferent to epinephrine and norepinephrine without pretreatment with dihydroergotamine. Augustinsson *et al.* (110) found that the hagfish *Myxine* differs from other vertebrates in that it apparently possesses no cardiac innervation. The lamprey *Lampetra*, on the other hand, has a bilateral cardiac branch from the vagus, and a large number of ganglion cells, nerve fibers and chromaffin cells in the myocardium. Acetylcholine has no influence on the noninnervated *Myxine* heart but accelerates that of *Lampetra*, an action which is blocked by hexamethonium. Baker & Baker (111,

112) have studied the electrogram changes in the frog heart induced by epinephrine, norepinephrine, and ouabain and (113) have presented evidence indicating that ouabain-induced electrical changes in the frog heart are antagonized by epinephrine and potentiated by calcium ions. Zamfir *et al.* (114) reported a decline in cholinesterase activity of the blood in digitalis poisoning. The cholinesterase content of dog ventricular muscle after bilateral ligation of the ureters was found to be depressed below normal levels, according to Gertler *et al.* (115), who suggested that the ECG changes seen in uremia could be accounted for on this basis. The excitability of the isolated toad heart perfused with anticholinesterases was investigated by Piva (116).

Brown (117) analyzed further the mechanisms responsible for the disorders of excitation and conduction in the heart when the dog is suddenly subjected to normal inspiratory pCO_2 after prolonged periods of previous exposure to high alveolar pCO_2. The plasma $[K^+]$ rises with high CO_2 breathing, but the increase is much less than that necessary to induce cardiac irregularities in dogs breathing room air. Lower plasma $[K^+]$ levels were able to cause ventricular fibrillation when associated with rapid declines in alveolar pCO_2. Thus a combination of a relatively high plasma $[K^+]$ and a rapidly falling plasma pCO_2 are essential to the induction of this type of spontaneous ventricular fibrillation. Trethewie & Hodgkinson (118) reported that an increase in pCO_2 is associated with heightening of the T wave in the cat heart. The coronary flow changes in the same direction as the T wave, but artificially imposed changes in coronary flow do not cause similar changes in the electrogram. Using isolated rabbit atria bathed in carefully adjusted bicarbonate-buffered solutions, Vaughan Williams (119) found that the force of contraction was positively correlated with the pH of the bathing fluid, while the conduction velocity was correlated with the pCO_2. Scherf *et al.* (120) have reported that hyperventilation temporarily diminishes or abolishes paroxysmal ventricular tachycardia and certain other arrhythmias. The administration of sodium lactate in 1.0 or 0.5 *M* solution was reported by Bellet *et al.* (121) to be efficacious in increasing the idioventricular rate in complete heart block. Hall (122) found that the embryonic rat heart would beat up to 22 minutes at pH 4–6 in HCl-Ringer, indicating a greater tolerance than is reported for mature heart muscle.

Studies on the turtle auricle by Tenney & Wedd (123) showed that under the influence of aconitine a properly timed stimulus may initiate a multiple response which appears like ordinary fibrillation or flutter. The role of impulse re-entry in the production of cardiac arrythmias was studied by Wedd & Tenney (124) and by Langendorf *et al.* (125) and Langendorf & Pick (126). Mendez & Rodriguez (127) found that sparteine, which increased the refractory period and accelerated conduction, abolished experimental atrial flutter in dogs. Loomis & Krop (128) induced atrial flutter and fibrillation in dogs, goats, and monkeys by administration of acetylcholine or vagal stimulation after pretreatment with an anticholinesterase. Atropine abolished the fibrillation. Roberts *et al.* (129) found that certain curariform drugs protect the

cat heart against epinephrine-induced arrhythmias. Di Palma (130) found that an aromatic quarternary ammonium compound with weak ganglionic and neuromuscular blocking effects raises the threshold for atrial fibrillation in the cat. Winbury & Hemmer (131) reported that quinidine, procaine amide, and several other compounds with antifibrillating action all increased the effective refractory period of isolated papillary strips from dog heart. Studies were reported by Harris & Bisteni (132) on the effects of sympathetic blockade drugs on ventricular tachycardia induced by myocardial infarction in dogs. Methoxamine protected the dog heart against ventricular tachycardia and fibrillation induced by epinephrine and cyclopropane or chloroform, according to Lahti *et al.* (133). Charlier & Vandersmissen (134) reported that L1906, a diphenylbutylamine derivative, protects against atrial and ventricular fibrillation under several circumstances. The actions of antihistaminic drugs and a local anesthetic in preventing ventricular arrythmias in the rat were studied by Malinow *et al.* (135, 136). Nuperaine HCl applied intrathecally prevented irregularities after $CaCl_2$ administration. The ventricular fibrillation induced by local cooling may be promoted by acetylcholine or prostigmine in dogs, according to Scherf *et al.* (137). Di Palma (138) studied the latent and refractory periods in relation to temperature.

Using the cat papillary muscle preparation to study the effects of rate of contraction upon contractile force in myocardium, Garb & Penna (139) found that when an extra beat is interpolated between regularly spaced contractions there is an augmentation of the next few succeeding beats and that the maximum augmentation occurs if the extra systole is thrown in early. In a study of cat papillary muscle strips, Cattell & Gold (140) presented evidence that the staircase phenomenon and the augmented response following closely paired stimuli are related phenomena. Rosin & Farah (141) presented evidence that a potentiating substance accounts for the phenomena of treppe and poststimulation potentiation. Frolkis (142) studied the mechanical work performed by heart muscle under various conditions and found that in the hypodynamic state there is a decreased amplitude when the rate of contraction is increased, in contrast to the staircase-like phenomenon observed in fresh hearts. Miledi (143) noted a "staircase effect" with moderate increase in stimulus frequency and a decreased mechanical response at higher rates in tortoise ventricle.

Coraboeuf *et al.* (144) recorded prepotentials from heart muscle at the site of propagated impulses, which are not seen at a distance from the focus of origin and which they associate with the pacemaker function. With ultramicroelectrode recording, West (145) identified the pacemaker area of the rabbit atrium as lying in the band of tissue separating the two caval orifices, and as showing a diastolic prepotential with slow depolarization and repolarization. Kosterlitz *et al.* (146) found that veratramine inhibited the activity of the sinoatrial pacemaker in spinal cats with denervated hearts. Krayer *et al.* (147) found that veratramine acts to lower the rate of the sinoatrial node, and that the effect is not abolished by atropine. Castillo & Katz

(148) confirmed the Gaskell phenomenon of a positive variation (hyperpolarization) of the injury potential during excitation of the inhibitory (vagal) nerve fibers to the heart of the frog. Borduas *et al.* (149) reported that atrioventricular node injury by chemical means in dogs shortens the P–R interval. Ouabain was found by Rand *et al.* (150) to potentiate the atrioventricular blocking action of adenosine in the guinea pig heart. Statistical studies of time relations between electrical and mechanical events in heart contraction in man were published by Braunwald *et al.* (151). Rosa (152) reported studies on superimposed recording of heart sounds and the electrocardiogram in relation to the problem of the time of the first heart sound relative to the QRS complex.

Rinaldi (153) presented a mathematical analysis of the polarized membrane and the central dipole treatments of electrocardiographic theory. Scher & Young (154) made 16 simultaneous recordings of action potentials in the heart of the dog indicating transmural conduction velocities of 0.3 m. per sec. for Purkinje tissue. Using the spatial vectorcardiogram technique, Simonson *et al.* (155) have studied the speed of ventricular activation. Taking the angular speed in the central segment of the spatial QRS loop they found two degrees per msec. in normals and significantly less in patients with conduction defects. Kossmann *et al.* (156) attempted to calculate from vectorcardiograms the electrical energy expended in depolarizing and repolarizing the myocardium.

Schmitt & Simonson (157) reviewed the present status of vectorcardiography. They pointed out that scalar, plane-vector, and space-vector electrocardiography can now be studied without the element of spatial distortion and that it should soon be possible to answer such questions as which method gives rise to the most useful diagnostic clinical data. They suggested that time-based and spatial vector methods each contribute information which would be difficult to obtain by the other, but that only future study will determine whether either method can ultimately be made adequate without assistance from the others. Bayley (158) investigated further the problem of the zero of potential of the heart's field and the discrepancies between homogeneous torso models and the intact subject. Frank (159) reported on the measurement and significance of cancellation potentials on the human subject. Bladier & de Comnene (160) have described methods for recording an amplified derivative of the P wave. Lown *et al.* (161) showed that patients with Cushing's syndrome have short P–R intervals and those with Addison's disease long intervals, indicating direct or indirect effects of the adrenal steroids on the excitatory process. Hall *et al.* (162) reported on ECG studies of effects of desoxycorticosterone which are potentiated by NaCl and reversed by KCl feeding. The effects upon the ECG of $NaBO_3$ by intravenous injection in man were noted by Conn *et al.* (163), who found ST segment depression. Statistics were given by Herndon *et al.* (164) on the correlation of ECG changes and plasma ion and nonprotein nitrogen levels in 663 observations on 61 patients. Only K^+, Ca^{++}, and PO_4 levels were strongly correlated with

ECG changes. Wenger *et al.* (165) reported on esophageal electrocardiography, particularly after atrial injury. Atrial flutter was studied with endocardial and esophageal leads by Giraud *et al.* (166). The duration of the Q–T interval has an inverse relation to the heart rate, but according to Klakeg *et al.* (167) the scatter is very marked and other factors than heart rate are frequently the more active determinants. Gross (168)considered the relation of Q–T interval to the circle hypothesis of cycle duration.

Stein *et al.* (169) and Hazard *et al.* (170) studied the influence of lithium chloride on the isolated perfused frog heart. Kleinfeld *et al.* (171) reported on the effects of Cd^{--} on the electrical and mechanical activity of the frog heart. The influence of Mg^{++} on the ECG of the dog was studied by Merklen *et al.* (172). The effects of Ca^{++} on cardiac rhythm were studied by Winbury & Hemmer (173). When combined in the ethylenediaminetetracetate (EDTA) chelate complex, calcium does not exhibit the cardiotonic effect on the hypodynamic heart which is seen when readily dissociable calcium salts are administered, according to Rothlin *et al.* (174). Other evidence indicates that the calcium ion activity is reduced to very low levels in the presence of EDTA. St. George *et al.* (175) reported that bilateral adrenalectomy did not significantly alter myocardial potassium in rats. Page & Real (176) reported studies on interrelations of Ca^{++}, K^{+} and ouabain effects on cardiac function. Benthe (177) reported studies on the effects of changes in $[K^{+}]$ and $[Ca^{++}]$ upon conduction rate in the frog heart. The influences of changes in $[K^{+}]$ in blood and heart muscle on the duration of systole (phonogram) and the electrocardiogram were studied by Kühns (178) in dogs and rats. Bellet (179) reviewed the literature on the effects of changes in $[K^{+}]$ on the electrocardiogram and other aspects of heart activity. Loewi (180) found that NaF and Na oleate restore amplitude in the depressed frog heart preparation and suggests that they may restore the normal susceptibility of the heart to calcium. The effects of $C Cl_4$ poisoning on the ECG were reported by Arrigo & Paoletti (181). Marshall (182) studied the effects of various metabolic inhibitors on the electrogram of the isolated turtle ventricle. Lombard & Witham (183) and Fabre *et al.* (184) have reported great variability in ECG characteristics in normal dogs (90 and 50 studied, respectively) including changes which would indicate abnormality in man.

Cardiac reflexes.—Coleridge & Linden (185, 186) showed that the rate of filling of the right atrium is important to the regulation of heart rate by the Bainbridge reflex. A. and E. Struppler (187) suggest that the rate of change of pressure determines the discharge frequency of vagal afferents in the atria. Further studies on receptors in the atria and ventricles of the cat heart employing records of impulses in single afferent fibers were reported by Paintal (188). He found that the discharge rate of the ventricular receptors increases sharply in early systole and that the minimum rate is increased by veratrum alkaloids. The Bezold reflex is considered to be mediated through these fibers. Reed & Scott (189) found a smaller decline in heart rate upon carotid sinus compression in dogs breathing oxygen than when breathing air. They also

found (190) that bilateral stimulation of carotid sinus receptors produced effects greater than the sum of effects of individual stimulation of each sinus and that the right produces greater effects than the left. Levy *et al.* (191) found that the rise in arterial pressure after moderator nerve section was not associated with an increase in cardiac output, indicating rather that arteriolar constriction causes this type of hypertension.

Reflex vagal slowing of the heart by chemical stimulation of receptors in the larynx was studied by Kisch & Yuceoglu (192). It was reported by Enikeeva (193) that the respiratory cyclic changes in heart rate begin in puppies at $2\frac{1}{2}$ months, while the pulse rate declines from around 200 per minute at birth to adult values at 11 or 12 months. Meulders (194) recorded a cessation of action potential volleys in the cervical sympathetic nerve occurring during the phase of active volleys in the phrenic nerve.

Temperature and heart function.—Nardone (195) studied the difference between simple hypothermia and hibernation in the arctic ground squirrel, reporting significant differences in the electrocardiogram in the two situations. Serial electrocardiographic studies were made in ground squirrels and hedgehogs in relation to hibernation by Dawe & Morrison (196), who found that the heart rate fell more rapidly than the body temperature did during induction of hibernation and rose much more abruptly than the temperature did in arousal. It would appear that the heart rate change is part of a mechanism fundamental to the hibernation state and not simply a function of temperature. Bïorck & Johansson (197) reported electrocardiographic studies at various lowered temperatures in fishes, frogs, hedgehogs, and dogs, and compared the findings with those in hypothermia in man. Siems *et al.* (198) reported ECG data on dogs exposed to hypothermia. Tysinger *et al.* (199) showed that dogs, the circulation of which is maintained by a pump-oxygenator, survive exposure to temperatures as low as 1.5°C. for 30 minutes without heart damage or other sequelae. Cooling the dog to 25°C. results in a fall in threshold of excitability of the ventricle unless the blood pH is maintained constant, by artificial respiration, according to Covino & Hegnauer (200). When pH is controlled the duration of systole and the total refractory period are prolonged but excitability is otherwise not greatly altered. They (201) reported that respiratory acidosis in hypothermia is majorly responsible for the excitability changes observed when pH is not controlled. They (202) also studied electrolyte exchange between coronary blood and heart muscle in hypothermic dogs and reported that development of ventricular fibrillation at low body temperature was associated with movement of Ca^{++} into the myocardium. Cookson & Di Palma (203) reported studies on the bradycardia of profound hypothermia in the dog. Montini & Paoletti (204) studied the isolated rabbit heart at various temperatures and reported greater sensitivity to epinephrine and acetylcholine at lower temperatures. According to their findings (205), previous lowering of the temperature of the whole animal before isolation protected the isolated heart against arrhythmia. Hollander & Webb (206) studied the influence of temperature upon mechanical and ex-

citatory processes in rat atrium. Marshall & Vaughan Williams (207) reported that when isolated rabbit atrium is cooled to 14° to 20°C. all electrical and mechanical signs of activity cease. Upon gradual rewarming small rhythmic potentials appear before measurable tension production. In this state the addition of 10^{-6} gm. per ml. of acetylcholine to the perfusate causes an immediate appearance of tension development and an increase in the magnitude of the potentials. McCrory & Virtue (208) found fewer dogs developed ventricular fibrillation in hypothermia when anesthetized with pentobarbital than with cyclopropane. Edwards *et al.* (209) found a decline in coronary blood flow and a drop in myocardial oxygen consumption in dogs subjected to immersion hypothermia. Badeer (210, 211) reported that the coronary flow in the heart-lung preparation is not reduced by cooling the heart, showing that myocardial hypoxia is not the necessary cause of arrest in hypothermia. Sabiston *et al.* (212) noted reduction in cardiac output, heart rate, and coronary artery flow upon cooling dogs to 25°C. The fraction of the cardiac output perfusing the myocardium increased.

Cardiohemodynamics

The measurement of cardiac output.—The magnitude of the error encountered in estimating the cardiac output by the Fick method attributable to periodic variations in blood flow rate and in oxygen (or dye) content of the blood at the locus of sampling was studied by Wood *et al.* (213). The question of the magnitude of cyclic oxygen content fluctuations during a period of observation was approached by the use of a sampling technique which allowed blood to be withdrawn at predetermined phases of the cardiac and respiratory cycles, and by continuous withdrawal at a rapid rate through a recording cuvette oximeter. The authors found respiratory variations of 1 to 2 per cent in the oxygen saturation of pulmonary artery blood in the normal subject breathing slowly at rest. They also measured the "smearing" effect of longitudinal mixing in long tubes on the apparent amplitude of cyclic variations. At 15 cycles per minute in their measuring system the amplitude of a recorded fluctuation is only 20 per cent of the real variation. Thus the real fluctuations in "mixed" venous blood oxygen content during a respiratory cycle are larger than those recorded. Under the conditions employed, the authors calculate that the error in the cardiac output estimate due to this cause is only 4 per cent, but they point out that in exercise it might become large. In exercise they reported an increase in amplitude of the respiratory wave of pulmonary artery blood oxygen saturation. Hubay *et al.* (214) showed that in positive pressure artificial respiration the reduction of pulmonary artery flow during insufflation is due mainly to increased resistance to flow in the pulmonary vascular bed. Howard *et al.* (215) showed that respiratory variations in cardiac output may influence the time course of concentration of dye in arterial bood. Consecutive estimates of cardiac output at two minute intervals in the dog, using the constant infusion para-aminohippuric acid method, were made by Vidt *et al.* (216), who found fluctuations

between 3.06 and 9.521 per min. in 10 such measurements. Fowler & Mannix (217) showed that the Gorlin formula for calculating the magnitude of shunts gives poor correlation with measured sizes of the ductus arteriosus in 12 cases, as might be expected from the inability of the Fick method to deal in practice with instantaneous values.

Huff *et al.* (218) found close correlation between calculated cardiac outputs using the conventional oxygen Fick method and one employing radioiodinated albumin and a scintillation detector. The dye-dilution curve method of cardiac output determination was subjected to further analysis by Dow (219), who suggested an empirical formula to replace the measured area in the conventional output formula. Using constant-rate and sudden single injection methods, Shepherd *et al.* (220) found no consistent differences between the two, or between them and the oxygen Fick values in patients with various diseases and in normal subjects totalling 17 individuals. The use of the disappearance curve of infused para-aminohippuric acid which does not require cardiac catheterization for the determination of cardiac output in man, along with renal clearance studies, was reported by Hendricks *et al.* (221). Indigo carmine was suggested for dye dilution studies of cardiac output by Lacy *et al.* (222) because it is rapidly cleared from the blood by the liver and kidneys and thus may be useful for repeated measurements. A rapid blood sample collector for use in the dye dilution method of estimation of cardiac output was described by Rothe & Sapirstein (223). A modified colorimeter for blue dye T-1824 registration in whole blood has been described by Falholt & Kaiser (224).

Talbot & Harrison (225, 226, 227) reported experimental comparisons of current ballistocardiographic methods. They pointed out that advantages are gained when the resonance of the system is set below the BCG spectrum but that the derivation of cardiovascular forces from body motions would be improved by reducing the forces from the support for the body. Tobin *et al.* (228) employed electrical filtering of body resonance distortion. Starr (229) reported studies on cadavers with simulated cardiac ejection accomplished with a mechanically driven piston pump. Grandell (230) reported on cadaver studies of ballistocardiography recording natural frequencies and damping in three planes of oscillation. De Simone *et al.* (231) evaluated the K constant of Bazett's formula from data on normal subjects. Morris & Braunstein (232) reported a conspicuous transverse component in the frontal plane VBCG not seen in normals.

Fredrick *et al.* (233) studied the ballistocardiogram of the normal dog and found the configurations similar in general to those in man, and largely unaltered by opening the chest. Thomas *et al.* (234) found very complex changes in the ballistocardiogram in the dog after occlusion of the venae cavae, pulmonary artery, or aorta. They conclude that muscular forces other than those associated with ejection of blood are of high importance to the form and amplitude of the body movements.

The uses and limitations of the pressure pulse contour method of estimat-

ing cardiac output were discussed by Remington (235), who pointed out the relatively large errors found by present methods. Ronninger (236) suggested mathematical refinements in stroke volume estimations by the pressure pulse contour method. Giulio (237) studied the cardiopneumogram quantitatively and has concluded that it is not possible to estimate cardiac stroke volume from such measurements.

Mechansisms of adaptation to load.—Sarnoff (238) reviewed the diastolic volume-energy production relationships in heart muscle. He pointed out that the stroke work at a given left atrial filling pressure, which may be assumed under certain circumstances to be the dominant determinant of left ventricular volume, can be made to vary with changes in heart rate by infusion of epinephrine or by changes in coronary perfusion. He also noted that for each new condition changes in filling pressure influence the stroke work as would be predicted from the diastolic volume law. Berglund (239) pointed out that in modern terminology the diastolic volume-ventricular work relationship provides a simple servomechanism for maintaining a balance between cardiac filling and output. Price & Helrich (240) suggested that the "competence index" of the heart depends upon the slope of the curve relating cardiac output changes to right atrial pressure changes. Rushmer (241) measured length and circumference changes of the left ventricle in contraction in the intact dog using strain gauge methods and has found that both dimensions decrease in systole. Bayliss (242) reported a mechanical model of the heart which obeys the "law of the heart" as to relations between several but not all important variables. Klepzig (243) reported on the response of the normal and pathological human heart to load, using cardiac catheterization, the roentgenkymograph, and other techniques. Björk & Malmström (244) recorded left and right atrial pressures by direct puncture and catheter, respectively, in relation to the Valsalva maneuver reporting a fall in left atrial pressure.

Salisbury (245) found that the maximum systolic pressure which can be developed by the right ventricle under isometric conditions is almost a linear function of the coronary arterial perfusion pressure at the time over a large range of perfusion pressures. Hild & Sick (246) studied the left ventricle in an isolated heart perfused through its coronary arteries, observing increased diastolic elasticity when slightly hypertonic salt solutions are used for perfusion.

Since the pericardium is a limiting factor to right heart filling when acute left heart dilation has occurred, Berglund *et al.* (247) have suggested that it may serve to limit elevation of pulmonary capillary pressure in left heart failure and thus protect against pulmonary edema. Isaacs *et al.* (248) showed that cardiac tamponade produced in dogs by injecting air or saline into the pericardial sac induced the characteristic lowered cardiac output entirely by decreasing the effective filling pressure of the heart.

Cotton & Pincus (249) and Hilton (250) compared the effects of *l*-epinephrine and *l*-norepinephrine on the contractile force of the heart *in situ*

and found generally similar effects of the two substances on augmentation of tension. Studies were reported by Hild & Herz (251) indicating that epinephrine causes a decrease in elasticity during diastole at high heart rates, due presumably to more rapid relaxation, which permits greater filling at a given venous pressure. Herz (252) also reported decreased duration of contraction and relaxation phases after epinephrine.

Burn *et al.* (253) made the interesting observation that in the isolated dog heart-lung preparation, driven electrically at rapid rates, the cardiac output at constant filling pressure increases when partial atrioventricular block occurs. This effect is presumably to be related in part to the longer interval allowed for ventricular filling. When atrial fibrillation occurs at very high heart rates (250 per min.) there is a similar improvement in cardiac output, also associated with ventricular slowing. Harvey *et al.* (254) studied patients with atrial flutter and found that when conversion to a normal sinus rhythm was achieved there was an increase in cardiac output. Storstein & Tveten (255) reported on changes in cardiac output in patients with atrial fibrillation following quinidine therapy. Their results showed no consistent change in cardiac output, but the variability in heart rate changes precludes the possibility of drawing any conclusions as to the role of atrial contraction in the efficiency of the heart as a pump. Starzl *et al.* (256) induced complete heart block in dogs and found that cardiac outputs and coronary flows were lower than before injury.

Starzl & Gaertner (257) have described methods for inducing heart failure in dogs, utilizing surgically induced heart block and graded enforced exercise. Repetitive electrical stimulation of the ventricles at rapid rates in normal dogs can lead to a fall in cardiac output and a rise in venous pressure, according to Starzl *et al.* (258).

Guyton *et al.* (259) reported a mathematical circuit analysis of the major circulatory factors controlling venous return to the heart which was shown to satisfy some experimental tests. Freis *et al.* (260) described a method for substituting a mechanical pump for the left ventricle in studies of regulatory mechanisms. Rose *et al.* (261) used this device to demonstrate a direct vasoconstrictor effect of epinephrine and norepinephrine on the pulmonary vascular bed. Sunahara *et al.* (262) reported studies of right atrial pressure and cardiac output in dogs in relation to intravenous infusion of plasma,whole blood and packed erythrocytes. According to Gowdey (263), the increased cardiac output seen with hypervolemia induced by plasma infusion may be reversed by injecting packed red cells, indicating that the blood oxygen capacity is a factor in controlling cardiac output. Gowdey *et al.* (264) studied infusions of gum acacia solutions with results as to cardiac output and right atrial pressure similar to those obtained with plasma. Gowdey & Young (265) reported also on dextran infusions in dogs. Ferguson *et al.* (266) found that in dogs with large arteriovenous anastomoses the rise in cardiac output seen normally following large saline infusions did not occur, despite a rise in left ventricular end-diastolic pressure.

Donald *et al.* (267) studied cardiac output in exercise by pulmonary artery catheterization and the standard Fick oxygen techniques in bicycle ergometer exercise in 16 normal subjects. A correlation was established between the calculated cardiac index and the oxygen uptake. There was no simple relation found between the arteriovenous oxygen difference and the cardiac output. The cardiac index of athletes was studied by Freedman *et al.* (268) using cardiac catheterization and the conventional oxygen Fick method. In subjects with resting cardiac indices between 2.8 and 3.6 l. per min per m^2 they found the calculated cardiac output to increase with exercise to values of 10 l. per min. per m^2 when the body oxygen consumption rose from 150 to 1100 cc. per min. per m^2. The correlation between oxygen use and cardiac output in exercise was found not to be different in trained athletes and in the normal subjects studied by Donald *et al.* (267). The arteriovenous oxygen difference appears to increase with increasing cardiac output in exercise similarly in trained and in untrained subjects. The subject of cardiac output and its control during muscular work was reviewed by Asmussen & Nielsen (269). It was pointed out that in the intact circulation an increase in cardiac output can occur without increase in diastolic ventricular volume if either the heart rate increases or the work capacity of the ventricular muscle is increased, as by the action of epinephrine. The major unsolved problem was pointed out to be the mechanism for increased venous return.

The effects of thiamine, riboflavin, and alloxazine mononucleotide on the oxygen debt after exercise were studied by Poppi *et al.* (270) in 20 cardiac patients. They reported a reduction with each of the agents. Theilen *et al.* (271) reported on studies of persons acclimatized to life at high altitudes (14,900 ft.) and at sea level. The higher cardiac output at rest found in the former would be expected as a part of the acclimatization mechanism, while the greater maximum output in exercise may be an evidence of cardiac hypertrophy.

An interesting contribution to the study of the mechanisms involved in cardiac hypertrophy was made by Kokas *et al.* (272). They found that when rats are made to swim till exhausted, which treatment was known to induce cardiac hypertrophy after ten days, the administration of adenosine triphosphate, or another purine nucleotide identified as a guanilic acid derivative was found to prevent the heart hypertrophy. These agents increased the swimming time over that of saline injected controls. Earlier work had also established that adrenal gland hypertrophy results from such enforced exercise. These authors showed that administration of the nucleotides also eliminates the increase in adrenal weight.

Luisada & Diamond (273) reported striking differences among thirteen cardiac glycosides as to their effects upon diastolic length (elasticity) in ventricular strips. Most glycosides caused diastolic shortening at clinically useful concentrations. Leüsen *et al.* (274) reported studies on acetyldigitoxin using papillary muscle strips. Fawaz (275) reported that the effects of quinidine, mersalyl, and procaine amide on the lethal dose of ouabain in the dog heart-

lung preparation are very small or zero. Various coronary dilating substances were found by Dörner (276) to increase the toxicity of strophanthin in dogs and guinea pgis. Gruhzit & Farah (277) found that epinephrine still had positive inotropic effects when ouabain was ineffective in countering the action of large doses of cyanide, azide, or 2,4-dinitrophenol.

According to Rothlin *et al.* (278), the work performed by the isolated heart (heart-lung preparation) at various right atrial filling pressures is greatly reduced by dinitrophenol at 1.14×10^{-4} *M* concentration. This effect is reversed by lanatoside C, 0.4 mg. per 100 gm. heart weight when the oxygen supply is adequate but not otherwise. The increase in heart oxygen consumption produced by dinitrophenol is not reversed by the digitalis glycoside.

Berman & Saunders (279) reported that the hypodynamic rat ventricle strip shows recovery of contractile activity upon addition of various substrates, pyruvate, lactate, β-hydroxybutyrate, acetate, succinate, and glucose, the effectiveness usually declining in the order given when phosphate buffered salt solutions were employed. At lower temperatures the magnitude of the inotropic effect of added glucose in the isolated papillary strip is greater, according to Garb & Scriabine (280). Garb *et al.*[(281) also found marked species differences in responsiveness to glucose, the rat heart showing a greater effect than the guinea pig, rabbit, and cat hearts.

The actions of adenine, adenosine, and adenosine mono- di-, and triphosphates on Langendorff preparations of rat and guinea pig hearts perfused with Ringers fluid were studied by Chevillard & Guerin (282). They found that adenine was nearly inactive, but that the other derivatives all had rate-slowing effects at concentrations of 1×10^{-8} *M* or more.

The coronary blood flow.—Using a preparation in which systemic blood is shunted around the right atrium and ventricle, the coronary blood flow was measured as the total right ventricular output in the dog by Alella *et al.* (283). They found an increase in coronary flow associated with an elevation of aortic pressure and with increased cardiac output, but the differences in the latter case were not statistically significant. A. M. Katz *et al.* (284) correlated coronary flow with arterial blood pressure and cardiac output and found correlation of cardiac output with coronary flow at higher blood pressures but not at lower. Case *et al.* (285) measured the factors involved in total coronary vascular bed resistance in the dog and found the resistance to be positively correlated with the hematocrit. A. M. Katz *et al.* (284) have also published data which indicate that dilution with dextran solutions lowers coronary vascular resistance. Katz *et al.* (286) measured cardiac output, arterial pressure, total coronary flow, and cardiac oxygen consumption in dogs with systemic blood shunted around the right heart. They found cardiac efficiency to increase in general with increasing heart work, but not with increasing arterial pressure when the cardiac output was above 1 l per min. Harris & Summerhayes (287) studied pressure variations in the great cardiac vein and found elevations during systole. These observations correlate with increased coron-

ary venous outflow in systole, presumably related to myocardial intramural tension changes.

Case *et al.* (288) studied coronary flow and ventricular function in hearts perfused through the left main coronary artery and have found that restriction of left coronary flow greatly reduces the work that the left heart is able to perform at a given left atrial filling pressure. By contrast, the right ventricular stroke work capacity is unimpaired. The left atrial pressure, normally higher than the right, becomes very much more elevated at higher cardiac inflow rates when left myocardial ischemia is imposed. Lasker *et al.* (289) found that ethyl alcohol by intravenous infusion raised the coronary flow in the dog. A study on dogs by Hockerts & Mülke (290) on the effects of an anticoagulant drug, Tromexan, indicated some increase in coronary arterial flow rate without changes of venous or arterial pressure, or cardiac output. Rowe *et al.* (291) found administration of hydralazine was followed by a decline in calculated total coronary bed resistance and an increase in coronary flow in man, as measured by the nitrous oxide saturation method. Arnulf & Benichoux (292) reported that section of the preaortic plexus leads to coronary flow augmentation in the dog.

Meesmann & Schmier (293) investigated the oxygen content of arterial and coronary sinus blood, coronary sinus outflow rate, and right atrial pressure before, during and after compression of the right branch of the coronary artery. They found a significant decline in sinus outflow during right coronary occlusion within one minute, which they ascribed to decreased left ventricular work and oxygen consumption. The decline in coronary sinus outflow occurred in proportion to the rise in right atrial pressure. The relationship of the variable distribution of the branches of the coronary artery to the effects of occlusion of the several branches on heart function was studied by Meesmann & Schmier (294), who found that, when blood flow to only one chamber was compromised, only that chamber began to fail. They (295) also showed that left heart failure after restriction of coronary flow to the right ventricle could be considered as being secondary to the failure of the latter to fill the left heart.

The rise in serum glutamic oxalacetic transaminase following myocardial infarction was studied further by Lemley-Stone *et al.* (296), who found the elevation to be proportional to the size of induced infarcts in dogs, and further that the damaged muscle tissue lost enzyme. Similar results were reported by LaDue & Wroblewski (297) and Agress *et al.* (298). Nydick *et al.* (299) found that myocardial ischemia for 45 min. did not lead to a rise in serum enzyme levels but that 6 hrs. of flow stoppage produced the effect.

Linko & Waris (300, 301) investigated the plasma protein changes after acute myocardial infarction, studying α_2 globulin, fibrinogen, and mucoprotein. The erythrocyte sedimentation rate proved to be as reliable an indicator as the serum mucoprotein level. Increased urinary excretion of coproporphyrins after acute myocardial infarction was reported by Eskola *et al.* (302). Comparable increases were observed, however, after pulmonary em-

bolism. Fabre & Linquette (303) reported cross-circulation experiments on dogs in which they produced shock by ligation of coronary artery branches, indicating that the effects are not due to resorption of toxic substances from necrotic tissue.

Eckstein (304, 305) studied the frequency of functional and anatomical arterial anastomoses in the coronary system in pigs and dogs. Measuring the retrograde flow in the circumflex branch, he found that it was increased after a prolonged period of anemia followed by restoration of the normal hematocrit. Hearts with the larger retrograde flows (indicating more collaterals) tolerated coronary occlusion better, as judged by pathologic changes in the ECG, than did those with low retrograde flow rates. Temesvári (306) reported that coronary ligation is better tolerated in dogs after induction of pericardial adhesions with magnesium silicate talc than in normals. According to Milch *et al.* (307), thoracic sympathectomy or procaine injection into the left stellate ganglion in dogs exert significant protective effects against death from acute occlusion of the anterior descending branch of the left coronary artery. Struppler (308) was unable to find clear cut evidence of changes in action potentials in vagus afferent fibers from atria or ventricles following coronary artery ligation. He (309, 310) found in cats that the frequency of discharge from atrial fibers increased with a rise in venous or atrial pressure. Occlusion of coronary arteries was followed by a bradycardia, but the latter was not abolished by bilateral vagotomy and therefore cannot be ascribed to a vagal reflex. Wartman *et al.* (311) were unable to observe any effect of ACTH upon myocardial infarcts resulting from coronary artery branch ligation. Hepper *et al.* (312) reported slight effects of cortisone on the removal of necrotic cells in experimentally produced infarcts, but saw no differences at 60 days.

Teng & Heyer (313) presented a statistical treatment of data on the incidence of acute myocardial infarction occurring at times of different climatic conditions in a single locality. Calculations from 1,386 patients presenting the disease in a 5-year period show an increased (doubled) frequency of morbidity during the days of sudden onset of cold weather, which has a probability against chance occurrence of 10^{15} to 1. It is surprising that, although Hippocrates recognized correlations of disease with meterological factors 24 centuries ago, few studies of physiological mechanisms which may be involved have been made. Peel (314) studied age and sex factors in coronary disease. He reported a rise in incidence at middle age in males with a decline at older ages, which decline he did not find in females. Vague *et al.* (315) reported that women with coronary disease fell into a group with more masculine characteristics than did a group of controls.

Circulatory changes at parturition.—The hemodynamics of the closure of the foramen ovale were studied exhaustively by Dawes *et al.* (316). They found that in the fetal lamb the pressure in the vena cava generally exceeds that in the left atrium but that during atrial systole the pressure in the left atrium rises momentarily so that there could be temporary closure of the foramen ovale. However, when ventilation of the lung is begun the pressure

in the left atrium rises with increased pulmonary blood flow and the gradient across the foramen ovale is reversed within a few minutes and normally remains so, bringing about permanent physiological closure. Anatomical closure begins toward the end of the first week of life.

A phonocardiographic study of the murmur from the patent ductus arteriosus in new born lambs was reported by Dawes *et al.* (317), who noted that it occurs only when the ductus has constricted to a small diameter. Cineangiographic studies by these authors (318) showed the ductus to be patent many hours after birth. Oxygen content studies of blood from carotid artery, right ventricle, and pulmonary artery show that one-fourth to two-thirds of the pulmonary blood flow may pass through the ductus arteriosus from the aorta to the lungs. Temporary occlusion of the ductus after birth causes a fall in arterial oxygen saturation and it is suggested that temporary patency of the ductus arteriosus for some hours after birth serves a useful function while the lungs are not fully expanded and ventilated. Eldridge & Hultgren (319) have reported studies on the human newborn indicating that the shunt may persist in the opposite direction with significant frequency for up to 72 hours after birth. Presumably such a situation would occur only if pulmonary vascular resistance remained high for the period in question. Prec & Cassels (320) made dye dilution studies in newborn infants and found that before 15 hours post-partum there were evidences of left to right shunts indicating patency of the ductus arteriosus or a diphasic type of curve suggesting reversal of flow in the shunt.

The viability of newborn lambs under various circumstances and at various fetal ages was studied by Born *et al.* (321). They found a low distensibility of the lung in prematures (100/147 of full term) and also a small change in pulmonary vascular resistance upon inflation in prematures. Very abruptly, between the 100th and 110th days of gestation, the physiological characteristics of the lung change and viability improves. The morphogenesis of atrial septal defects was studied by Hudson (322).

Pathologic physiology.—The pressure gradients across interatrial septal defects in man were studied by Shaffer *et al.* (323), and found to be cyclic in form ranging from 10 mm. Hg (left atrium higher) to zero or even a reversal in sign during part of the cardiac cycle. Coelho *et al.* (324) studied pulmonary artery wedge pressures in 180 cases of lesions of the mitral valve. In 12 cases of mitral regurgitation verified at operation normal pulse waves were seen. Müller & Shillingford (325), using a double lumen catheter to act as a Pitot flow meter, found instances in which tricuspid regurgitation appeared to be equal to or greater than the forward flow. Changes in cardiac output, pressures, and other quantities, caused by exercise or administration of drugs including the digitalis glycosides, were presented in relation to various disease states by Varnauskas (326). Rose *et al.* (327) reinvestigated the problem of the role of right ventricular failure in the production of the signs and symptoms of congestive heart failure. Employing venopulmonary shunts in dogs

to by-pass the right ventricle, they showed that lung perfusion is inadequate in the absence of right ventricular propulsion. In previous studies in which the signs of congestive heart failure did not appear after attempts were made to destroy the right ventricular myocardium, the results were attributed to the maintenance of sufficient right ventricular function to propel the blood adequately under the conditions of lowered cardiac output encountered.

Cardiac output in pregnancy was studied by Hendricks & Quilligan (328). Brandfonbrener *et al.*, (329) on the basis of indicator dilution studies in 67 male subjects aged 19 to 86 years, concluded that the cardiac output declines with age. Landowne *et al.* (330) reported that in the same subjects that the total vascular resistance increases with age and that the relative central elasticity appears to treble between 20 and 80 years of age.

Fieldman *et al.* (331) studied the cardiac output and other variables in 13 human subjects during recovery from thiopental sodium and nitrous oxide anesthesia. Price & Helrich (332) and Boniface *et al.* (333) investigated the decrease in myocardial work capacity produced by various anesthetic agents. Bubnoff *et al.* (334) reported studies of the effects of K-strophanthin in reversing failure in the heart-lung preparation caused by somnifene. Greisheimer *et al.* (335) made dye dilution studies of cardiac output with several anesthetic agents. According to LaBarre & Garrett (336), R.P.2831 (heptaminol) exerts a positive inotropic effect upon the isolated heart depressed by barbiturates. Broustet *et al.* (337) found that acetyldigitoxin lowered pulmonary artery and wedge pressure regardless of whether or not a measurable increase in cardiac output occurred.

Gammill *et al.* (338), using dye dilution techniques to estimate cardiac output in 37 patients within 67 hours after the onset of myocardial infarction, found, as might be expected, normal values in many patients with elevated venous pressure. Bernath *et al.* (339) reported favorable palliative results from inferior vena cava ligation in severe intractible congestive heart failure in man. Davis *et al.* (340) studied congestive heart failure in dogs after constriction of the pulmonary artery and found that sodium retention was always associated with elevated central venous pressure. They (341) also found that digitoxin induced natriuresis only after the right atrial pressure began to fall. Some consequences of coronary artery narrowing upon liver blood flow have been studied by Meesmann & Schmier (342, 343). A post-mortem cinephotographic study of valve action in aortic stenosis was reported by McMillan (344). Harris (345) studied right ventricular pressure pulses with particular reference to shape in the presence of valvular stenosis and elevation of pulmonary artery pressure. Friese (346) reported studies on 57 normals and more than 100 pathological subjects in whom he recorded atrial pulsations across the esophageal wall, and found useful diagnostic information.

The greater part of the increased blood volume in cardiac decompensation was found by Nylin (347) to be in the increased residual volume of the heart. Hackel & Goodale (348) reported studies on the effects of hemorrhagic

shock on the heart, noting particularly a high oxygen extraction per unit work performed and a lowering of pyruvate uptake, or even a negative arteriovenous difference in the coronary blood.

Observations on heart sounds by spectral phonocardiography were reported by McKusick *et al.* (349, 350, 351), who presented data on the sound frequency characteristics of sounds related to aortic and mitral stenosis and insufficiency and other cardiac disorders. A method of vibration analysis of heart sounds was reported by Rodbard *et al.* (352). Studies on the origin of the physiologic third heart sound were reported by Dock *et al.* (353). X-ray and other observations led them to suggest that the sound originates in the tensing of atrioventricular valves by reflected waves during ventricular filling in its rapid phase.

King *et al.* (354) reported that diets containing ferrous iron and unsaturated fats lead to a myocardial fibrosis and fatal heart failure in mice which is preventable by supplementation with α-tocopherol or by removal of most of the unsaturated fat in the food. Tourniaire *et al.* (355) reviewed the literature on cardiac pathology in muscle dystrophies and reported observations on microscopic changes in heart muscle which may be related to alterations seen in the mouse in vitamin E deficiency. Myocardial fibrosis without coronary artery lesions was described in potassium deficiency by McAllen (356). The consequences of myocardial injury by chloroform and hypoxia were studied by Meesmann & Schmier (357). Hildes *et al.* (358) reported on 22 fatal cases of acute poliomyelitis in three quarters of whom myocarditis occurred, leading to left heart failure and pulmonary edema. Busch (359) reported refinements in methods of studying cardiac chamber mass in hypertrophy and reported concomitant histologic data.

Miscellaneous Observations

Harvey & Pieper (360) studied the distribution of C^{14}-labelled digitoxin in isolated perfused guinea pig hearts and found little in the mitochondrial fraction, more in the nuclear, and most in the cellular debris fraction after differential centrifugation. The "digitoxin space" was found to be smaller than the chloride space, indicating minimal intracellular binding. Okita *et al.* (361) studied blood levels of C^{14}-labelled digitoxin and its degradation products in eight patients. Carr *et al.* (362) reported on the effects of twenty vasoactive drugs upon the phosphokinase activity of coronary artery extracts.

Price *et al.* (363) used a needle biopsy technique to obtain samples of myocardium from dogs for use in electron microscopy. They showed that apparently intact and undistorted structures can be obtained by this means.

Becker (364) made histologic studies of myocardium of puppies born to mothers living at a simulated altitude of 20,000 ft. for two years. As compared with controls, there was an increase in the number of nuclei per unit volume and in their length and diameter.

In a study of 22 fetal and newborn human hearts, Lev & Lerner (365) were unable to find any evidence for muscular communications between

atria and ventricles outside the atrioventricular bundle of His. Prakash (366) adduced evidence that the specialized pacemaker and conducting structures in homoiothermal vertebrates have evolved from similar tissues present in the hearts of lower vertebrates. The heart and specialized conduction system of the frog tadpole have been investigated by the same author (367), as have the conducting tissues of the human embryo (368).

Hellman (369) reported the occurrence of spontaneous microscopic contraction waves in isolated mammalian heart muscle, even in single fibers, which are arrested by quinidine and procaine. Cavanaugh (370) studied spontaneous pulsation in trypsin-dissociated heart cells from four to six day chick embryos. The pulsation rate of isolated atrial cells is significantly higher than that of ventricle cells. Reaggregation occurs spontaneously and the cell pulsations become synchronous with a rate about equal to the average rate of the individual cells in the same culture. Foxon (371) presented an extensive review of the comparative anatomy and embryology of the vertebrate heart. A sequence of development of the cardiac contractile proteins was presented by Ebert *et al.* (372) with a duscussion of the possible metabolic bases of cardiogenesis. Sippel (373) studied the appearance of succinic oxidase activity in homogenates of rat and chick embryo ventricles and found that increments occur in two cycles in both forms. From further work (374) it appears that cholinesterase activity in a salamander (*Amblystoma*) heart is due to the specific type only; in the frog, chick, and rat both types are present.

Weidmann (375) studied Purkinje fibers with respect to the sodium transport mechanism and found evidence of an increase in sodium permeability during activation. Hercus *et al.* (376) showed that hypoxia increases the sodium uptake of resting myocardium and that stretching or stimulation of hypoxic muscle increases the uptake. At normal pO_2 stimulation does not have that result. McDowall *et al.* (377) studied right ventricular muscle strips from the rat heart under conditions of varying pO_2 and $[\dot{N}a]$. They found that such muscle can exert more tension after exposure to hypoxia when the $[\dot{N}a]$ is low than when it is high. They suggested that the metabolic requirements of a sodium pump mechanism may account for the observed effect.

BIBLIOGRAPHY

1. Maynard, D. M., Jr., *Biol. Bull.*, **104**, 156–70 (1953)
2. Maynard, D. M., Jr., *Biol. Bull.*, **105**, 367 (1953)
3. Maynard, D. M., Jr., *Biol. Bull.*, **109**, 420–36 (1955)
4. Hagiwara, S., and Bullock, T. H., *Biol. Bull.*, **109**, 341 (1955)
5. Krijgsman, B. J., Dresden, D., and Berger, N. E., *Bull. Entomol. Research*, **41**, 141–51 (1950)
6. Krijgsman, B. J., and Krijgsman-Berger, N. E., *Bull. Entomol. Research*, **42**, 143–55 (1951)
7. Bellemare, E. R., and Belcourt, J., *Can. J. Zool.*, **33**, 175–81 (1955)
8. Bekker, J. M., and Krijgsman, B. J., *J. Physiol. (London)*, **115**, 249–57 (1951)
9. Ripplinger, J., *Compt. rend. soc. biol.*, **147**, 333 (1953)
10. Euler, U. S. v., Chaves, N., and Teodosio, N., *Acta Physiol. Latinoamer.*, **2**, 101–06 (1952)
11. Divaris, G. A., and Krijgsman, B. J., *Arch. intern. physiol.*, **62**, 211–33 (1954)
12. Prosser, C. L., and Judson, C. L., *Biol. Bull.*, **102**, 249–51 (1952)
13. Kanungo, M. S., *Nature*, **176**, 980–81 (1955)
14. Alexandrowicz, J. S., *J. Marine Biol. Ass. U.K.*, **31**, 85–96 (1952)
15. Alexandrowicz, J. S., *J. Marine Biol. Ass. U.K.*, **33**, 709–19 (1954)
16. Alexandrowicz, J. S., *J. Marine Biol. Ass. U.K.*, **34**, 47–53 (1955)
17. Alexandrowicz, J. S., *J. Marine Biol. Ass. U.K.*, **31**, 563–80 (1953)
18. Alexandrowicz, J. S., and Carlisle, D. B., *J. Marine Biol. Ass. U.K.*, **32**, 175–92 (1953)
19. Needham, A. E., *Nature*, **173**, 272 (1954)
20. Ripplinger, J., *J. physiol. (Paris)*, **43**, 853–55 (1951)
21. Ripplinger, J., *J. physiol. (Paris)*, **45**, 227–31 (1953)
22. Jullien, A., and Ripplinger, J., *Ann. sci. univer. Besancon. zool. physiol.*, **1**, 35–77 (1954)
23. Jullien, A., Ripplinger, J., and Cardot, J., *Compt. rend. soc. biol.*, **148**, 1258 (1954)
24. Jullien, A., Ripplinger, J., Joly, M., and Vieille-Cessay, C., *Compt. rend. soc. biol.*, **149**, 722–23 (1955)
25. Ripplinger, J., and Mercier, J., *Ann. sci. univer. Besancon. zool. physiol.*, **1**, 133–55 (1954)
26. Jullien, A., Ripplinger, J., and Joly, M., *Compt. rend. soc. biol.*, **149**, 964–66 (1955)
27. Jullien, A., Ripplinger, J., and Joly, M., *Compt. rend. acad. sci.*, **240**, 911–13 (1955)
28. Jullien, A., Ripplinger, J., and Joly, M., *J. physiol. (Paris)*, **47**, 200–05 (1955)
29. Welsh, J. H., and Taub, R., *J. Pharmacol. Exptl. Therap.*, **103**, 62–73 (1951)
30. Welsh, J. H., and Slocombe, A. G., *Biol. Bull.*, **102**, 48–57 (1952)
31. Luduena, F. P., and Brown, T. G., *J. Pharmacol. Exptl. Therap.*, **105**, 232–39 (1952)
32. Zacks, S. I., and Welsh, J. H., *Biol. Bull.*, **105**, 200–11 (1953)
33. Welsh, J. H., and Taub, R., *Brit. J. Pharmacol.*, **8**, 327–33 (1953)
34. Ten Cate, J., and Reesinck, M. J., *Physiol. Comparata Oecol.*, **3**, 337–42 (1954)
35. Pilgrim, R. L. C., *J. Physiol. (London)*, **126**, 619–22 (1954)
36. Pilgrim, R. L. C., *J. Physiol. (London)*, **125**, 208–14 (1954)
37. Florey, E., *Biol. Zentr.*, **70**, 523–30 (1951)
38. Fänge, R., and Östlund, E., *Acta Zool.*, **34–35**, 289–305 (1953–54)

39. Östlund, E., *Acta Physiol. Scand.*, **31**, 1–67 (1954)
40. Erspamer, V., and Ghiretti, F., *J. Physiol.* (*London*), **115**, 470–81 (1951)
41. Bacq, Z. M., Fischer, P., and Ghiretti, F., *Arch. intern. physiol.*, **60**, 165–71 (1951)
42. Welsh, J. H., *Arch. exptl. Pathol. Pharmakol.*, **219**, 23–29 (1953)
43. Florey, E., and Florey, E., *Z. Naturforsch.*, **9B**, 58–68 (1954)
44. Welsh, J. H., *Federation Proc.*, **13**, 162–63 (1954)
45. Welsh, J. H., *Nature*, **173**, 955 (1954)
46. Fänge, R., *Experientia*, **11**, 156 (1955)
47. Jones, J. C., *J. Morphol.*, **94**, 71–123 (1954)
48. Haywood, C. A., and Moon, H. P., *J. Exptl. Biol.*, **27**, 14–28 (1950)
49. Millar, R. H., *Nature*, **170**, 851–52 (1952)
50. Tenney, S. M., *Physiol. Comparata Oecol.*, **3**, 286–306 (1953)
51. Burger, J. W., and Smythe, C. McC., *J. Cellular Comp. Physiol.*, **42**, 369–83 (1953)
52. Nutting, W. L., *J. Morphol.*, **89**, 501–97 (1951)
53. Silén, L., *Acta Zool.*, 35(1/2), 11–70 (1954)
54. Jullien, A., Ripplinger, J., Guyon, M., and Cardot, J., *Compt. rend. soc. biol.*, **146**, 1946 (1952)
55. Jullien, A., Ripplinger, J., and Guyon, M., *Ann. Sci. univer. Besancon. Zool. Physiol.*, **1**, 85–90 (1954)
56. Pigrim, R. L. C., *J. Exptl. Biol.*, **30**, 297–317 (1953)
57. Potter, G. D., *J. Cellular Comp. Physiol.*, **37**, 487–99 (1951)
58. Binet, L., Jullien, A., Ripplinger, J., and Cardot, J., *Compt. rend. acad. sci.*, **240**, 1294–96 (1955)
59. Jullien, A., Ripplinger, J., Cardot, J., and Rérat, D., *Compt. rend. soc. biol.*, **149**, 726–28 (1955)
60. Corda, M., *Arch. fisiol.*, **54**, 373–85 (1955)
61. Orser, W. B., and Brown, A. W. A., *Can. J. Zool.*, **29**, 54–64 (1951)
62. Beard, R. L., Chap. 9: "Circulation," 232–72, In: *Insect Physiology* (K. Roeder, Ed., Wiley & Sons, New York, N. Y., 1000 pp., 1953)
63. Krijgsman, B. J., *Biol. Revs. Cambridge Phil. Soc.*, **27**, 320–46 (1952)
64. Krijgsman, B. J., and Divaris, G. A., *Biol. Revs. Cambridge Phil. Soc.*, **30**, 1–39 (1955)
65. Harvey, S. C., *Am. J. Physiol.*, **183**, 559–64 (1955)
66. Janke, J., *Arch. exptl. Pathol. Pharmakol.*, **225**, 160–61 (1955)
67. Garb, S., Scriabine, A., Penna, M., and Fujimori, H., *J. Pharmacol. Exptl. Therap.*, **115**, 300–4 (1955)
68. Fleckenstein, A., Janke, J., Davies, R. E., and Krebs, H. A., *Nature*, **174**, 1081 (1954)
69. Neilands, J. B., *J. Biol. Chem.*, **208**, 225–30 (1954)
70. Benson, E. S., Hallaway, B. E., and Freier, E. F., *Circulation Research*, **3**, 215–20 (1955)
71. Benson, E. S., *Circulation Research*, **3**, 221–28 (1955)
72. Hawkins, L. W., and Smith, J. R., *Proc. Soc. Exptl. Biol. Med.*, **90**, 104–6 (1955)
73. Ranney, R. E., *Am. J. Physiol.*, **183**, 197–202 (1955)
74. Stutz, H., Feigelson, E., Emerson, J., and Bing, R. J., *Circulation Research*, **2**, 555–64 (1954)
75. Robb, J. S., and Mallov, S., *J. Pharmacol. Exptl. Therap.*, **108**, 251 (1953)

76. Kisch, B., *Exptl. Med. Surg.*, **13**, 404–28 (1955)
77. Kisch, B., *Exptl. Med. Surg.*, **13**, 9–16 (1955)
78. Kisch, B., *Pubbl. staz. zool. Napoli*, **27**, 160–67 (1955)
79. Kisch, B., and Philpott, D., *Exptl. Med. Surg.*, **13**, 63–72 (1955)
80. Holton, F. A., *Biochem. J.* (*London*), **61**, 46–61 (1955)
81. Lemberg, R., Bloomfield, B., Caiger, P., and Lockwood, W. H., *Australian J. Exptl. Biol. Med. Sci.*, **33**, 435–50 (1955)
82. Slater, E. C., *Biochem. J.* (*London*), **59**, 392–405 (1955)
83. Lorber, V., and Cook, M., *J. Biol. Chem.*, **215**, 823–32 (1955)
84. Mahler, H. R., *Federation Proc.*, **12**, 694–702 (1953)
85. Hele, P., *J. Biol. Chem.*, **206**, 671–76 (1954)
86. Cooper, W. G., *Anat. Record*, **123**, 103–19 (1955)
87. Paul, M. H., Theilen, E. O., Gregg, D. E., Marsh, J. B., and Casten, G. G., *Circulation Research*, **2**, 573–78 (1954)
88. Meyer, D. K., Russell, R. L., Platner, W. S., Purdy, F. A., and Westfall, B. A., *Proc. Soc. Exptl. Biol. Med.*, **90**, 15–17 (1955)
89. Russell, J. A., and Bloom, W. L., *Am. J. Physiol.*, **183**, 345–55 (1955)
90. Bloom, W. L., and Russell, J. A., *Am. J. Physiol.*, **183**, 356–64 (1955)
91. Murray, J. B., *Am. J. Physiol.*, **177**, 463–66 (1954)
92. Raab, W., and Gigee, W., *Circulation Research*, **3**, 553–58 (1955)
93. Raab, W., and Gigee, W., *Circulation*, **11**, 593–603 (1955)
94. Sobel, H., Myers, S. M., and Marmorston, J., *Circulation Research*, **3**, 454–58 (1955)
95. Johnson, I. S., and Leone, C. A., *J. Exptl. Zool.*, **130**, 515–54 (1955)
96. Ungar, I., Gilbert, M., Siegel, A., Blain, J. M., and Bing, R. J., *Am. J. Med.*, **18**, 385–96 (1955)
97. Lüllmann, H., *Arch. Kreislaufforsch.* **23**, 12–76 (1955)
98. Bing, R. J., *Circulation*, **12**, 635–47 (1955)
99. Von Korff, R. W., *J. Lancet*, **75**, 514–22 (1955)
100. Burn, J. H., and Walker, J. M., *J. Physiol.* (*London*), **124**, 489–501 (1954)
101. Burn, J. H., Vaughan Williams, E. M., and Walker, J. M., *Brit. Heart J.*, **17**, 431–47 (1955)
102. Burn, J. H., Vaughan Williams, E. M., and Walker, J. M., *J. Physiol.* (*London*), **128**, 277–93 (1955)
103. Glaesser, H., and Tedeschi, R. E., *Arch. intern. pharmacodynamie*, **101**, 200–04 (1955)
104. Burn, J. H., *Lancet*, **264**, 1161–64 (1953)
105. Spadolini, I., *Arch. fisiol.*, **55**, 171–79 (1955)
106. Rothschuh, K. E., *Pflügers Arch. ges. Physiol.*, **260**, 374–84 (1955)
107. Rothschuh, K. E., and Berkel, H. A., *Pflügers Arch. ges. Physiol.*, **261**, 24–31 (1955)
108. Westermann, E., *Arch. exptl. Pathol. Pharmakol.*, **225**, 109–10 (1955)
109. Holtz, P., and Westermann, E., *Arch. exptl. Pathol. Pharmakol.*, **225**, 421–27 (1955)
110. Augustinsson, K.-B., Fänge, R., Johnels, A., and Östlund, E. (In press—to be published 1956)
111. Baker, W. W., and Baker, J. M., *J. Pharmacol. Exptl. Therap.*, **113**, 132–39 (1955)

112. Baker, W. W., and Baker, J. M., *Arch. intern. pharmacodynamie*, **102**, 105–12 (1955)
113. Baker, W. W., and Baker, J. M., *Circulation Research*, **3**, 274–79 (1955)
114. Zamfir, C., Covasneanu, Z., Rusu, E., Zelter, E., and Clejan, L., *Revista fiziol. norm. patol.*, **1**, 85–101 (1955)
115. Gertler, M. M., Kream, J., and Hylin, J., *Proc. Soc. Exptl. Biol. Med.*, **88**, 439–40 (1955)
116. Piva, G., *Arch. fisiol.*, **55**, 200–17 (1955)
117. Brown, E. B., Jr., *Proc. Soc. Exptl. Biol. Med.*, **90**, 319–23 (1955)
118. Trethewie, E. R., and Hodgkinson, M. M., *Quart. J. Exptl. Physiol.*, **40**, 1–11 (1955)
119. Vaughan Williams, E. M., *J. Physiol. (London)*, **129**, 90–110 (1955)
120. Scherf, D., Goldfarb, M., and Bussan, R., *Circulation*, **12**, 271–77 (1955)
121. Bellet, S., Wasserman, F., and Brody, J. I., *Circulation*, **11**, 685–701 (1955)
122. Hall, E. K., *J. Exptl. Zool.*, **129**, 343–56 (1955)
123. Tenney, S. M., and Wedd, A. M., *Circulation Research*, **2**, 28–34 (1954)
124. Wedd, A. M., and Tenney, S. M., *Ann. Internal Med.*, **41**, 935–41 (1954)
125. Langendorf, R., Pick, A., and Winternitz, M., *Circulation*, **11**, 422–30 (1955)
126. Langendorf, R., and Pick, A., *Circulation*, **11**, 431–39 (1955)
127. Mendez, R., and Rodriguez, M. I., *Arch. inst. cardiol. Mexico*, **25**, 443–62 (1955)
128. Loomis, T. A., and Krop, S., *Circulation Research*, **3**, 390–96 (1955)
129. Roberts, J., Roy, B. B., Reilly, J., Garb, S., Riker, W. F., Jr., and Hashimoto, K., *J. Pharmacol. Exptl. Therap.*, **114**, 279–87 (1955)
130. DiPalma, J. R., *J. Pharmacol. Exptl. Therap.*, **113**, 125–31 (1955)
131. Winbury, M. M., and Hemmer, M. L., *J. Pharmacol. Exptl. Therap.*, **113**, 402–12 (1955)
132. Harris, A. S., and Bisteni, A., *Am. J. Physiol.*, **181**, 559–66 (1955)
133. Lahti, R. E., Brill, I. C., and McCawley, E. L., *J. Pharmacol. Exptl. Therap.*, **115**, 268–74 (1955)
134. Charlier, R., and Vandersmissen, L., *Arch. intern. pharmacodynamie*, **101**, 377–79 (1955)
135. Malinow, M. R., Batlle, F. F., and Malamud, B., *Arch. intern. pharmacodynamie*, **102**, 55–64 (1955)
136. Malinow, M. R., Batlle, F. F., and Malamud, B., *Arch. intern. pharmacodynamie*, **102**, 266–73 (1955)
137. Scherf, D., Bussan, R., Gittinger, W. C., and Torin, S., *Circulation*, **12**, 620–24 (1955)
138. DiPalma, J. R., *Am. J. Physiol.*, **180**, 96–100 (1955)
139. Garb, S., and Penna, M., *Am. J. Physiol.*, **182**, 601–06 (1955)
140. Cattell, McK., and Gold, H., *Am. J. Physiol.*, **182**, 307–10 (1955)
141. Rosin, H., and Farah, A., *Am. J. Physiol.*, **180**, 75–82 (1955)
142. Frolkis, V. V., *Fiziol. Zhur. U.S.S.R.*, **41**, 78–83 (1955)
143. Miledi, R., *Arch. inst. cardiol. Mexico*, **25**, 379–402 (1955)
144. Coraboeuf, E., Boistel, J., and Distel, R., *Compt. rend. soc. biol.*, **149**, 1138–42 (1955)
145. West, T. C., *J. Pharmacol. Exptl. Therap.*, **115**, 283–90 (1955)
146. Kosterlitz, H. W., Krayer, O., and Matallana, A., *J. Pharmacol. Exptl. Therap.*, **113**, 460–69 (1955)

147. Krayer, O., Arora, R. B., and Meilman, E., *J. Pharmacol. Exptl. Therap.*, **113,** 446–59 (1955)
148. Castillo, J. del, and Katz, B., *Nature*, **175,** 1035 (1955)
149. Borduas, J. L., Rakita, L., Kennamer, R., and Prinzmetal, M., *Circulation*, **11,** 69–88 (1955)
150. Rand, M., Stafford, A., and Thorp, R. H., *J. Pharmacol. Exptl. Therap.*, **114,** 119–25 (1955)
151. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. J., *J. Appl. Physiol.*, **8,** 309–14 (1955)
152. Rosa, L., *Z. Kreislaufforsch.*, **44,** 488–93 (1955)
153. Rinaldi, R., *Cardiologia*, **26,** 52–60 (1955)
154. Scher, A. M., and Young, A. C., *Circulation Research*, **3,** 535–42 (1955)
155. Simonson, E., Schmitt, O. H., Blackburn, H. W., and Levine, R. B., *Circulation Research*, **3,** 408–14 (1955)
156. Kossmann, C. E., Briller, S. A., and Marchand, N., *Circulation Research*, **3,** 203–09 (1955)
157. Schmitt, O. H., and Simonson, E., *Arch. Internal Med.*, **96,** 574–590 (1955)
158. Bayley, R. H., *Am. Heart J.*, **50,** 694–705 (1955)
159. Frank, E., *Circulation*, **11,** 937–51 (1955)
160. Bladier, B., and de Comnene, J. S., *Arch. maladies coeur et vaisseaux*, **48,** 470–75 (1955)
161. Lown, B., Arons, W. L., Ganong, W. F., Vazifdar, J. P., and Levine, S. A., *Am. Heart J.*, **50,** 760–69 (1955)
162. Hall, C. E., Diserens, H. W., and Hall, O., *Am. J. Physiol.*, **183,** 550–54 (1955)
163. Conn, H. L., Jr., Antal, B. B., and Farr, L. E., *Circulation*, **12,** 1043–1046 (1955)
164. Herndon, R. F., Meroney, W. H., and Pearson, C. M., *Am. Heart J.*, **50,** 188–202 (1955)
165. Wenger, R., Massumi, R. A., and Kuramoto, K., *Cardiologia*, **26,** 193–208 (1955)
166. Giraud, G., Latour, H., and Puech, P., *Arch. maladies coeur et vaisseaux*, **48,** 817–43 (1955)
167. Klakeg, C. H., Berry, A. M., and Burchell, H. B., *Am. J. Physiol.*, **179,** 159–64 (1954)
168. Gross, D., *Cardiologia*, **26,** 292–305 (1955)
169. Stein, E., Kleinfeld, M., Greene, H., and Meyers, S., *Am. J. Physiol.*, **183,** 121–24 (1955)
170. Hazard, R., Boissier, J. R., and Mouille, P., *Compt. rend. soc. biol.*, **149,** 245–49 (1955)
171. Kleinfeld, M., Greene, H., Stein, E., and Magin, J., *Am. J. Physiol.*, **181,** 35–38 (1955)
172. Merklen, F. P., Berthaux, P., and Maurat, J.-P., *Compt. rend. soc. biol.*, **149,** 330–33 (1955)
173. Winbury, M. M., and Hemmer, M. L., *Circulation Research*, **3,** 474–77 (1955)
174. Rothlin, E., Taeschler, M., and Cerletti, A., *Schweiz. med. Wochschr.*, **84,** 1286–1289 (1954)
175. St. George, S., Freed, S. C., Rosenman, R. H., and Winderman, S., *Am. J. Physiol.*, **181,** 550–52 (1955)
176. Page, E., and Real, J. D., *Circulation Research*, **3,** 501–5 (1955)
177. Benthe, H.-F., *Arch. exptl. Pathol. Pharmakol.*, **225,** 293–302 (1955)

178. Kühns, K., *Z. Kreislaufforsch.*, **44,** 4–22 (1955)
179. Bellet, S., "Les effets des modifications du potassium serique et tissulaire sur l'electrocardiogramme." *Physiopathologie du potassium.* (Editions du centre national de la recherche scientifique, Paris, France, 1954)
180. Loewi, O., *J. Pharmacol. Exptl. Therap.*, **114,** 90–99 (1955)
181. Arrigo, L., and Paoletti, G., *Arch. fisiol.*, **55,** 85–95 (1955)
182. Marshall, J. M., *Am. J. Physiol.*, **180,** 350–56 (1955)
183. Lombard, E. A., and Witham, C., *Am. J. Physiol.*, **181,** 567–74 (1955)
184. Fabre, H., Fabre, R., and Linquette, Y., *Arch. maladies coeur et vaisseaux*, **48,** 673–75 (1955)
185. Coleridge, J. C. G., and Linden, R. J., *J. Physiol. (London)*, **128,** 310–319 (1955)
186. Coleridge, J. C. G., and Linden, R. J., *J. Physiol. (London)*, **130,** 674–702 (1955)
187. Struppler, A., and Struppler, E., *Acta Physiol. Scand.*, **33,** 219–31 (1955)
188. Paintal, A. S., *Quart. J. Exptl. Physiol.*, **40,** 348–63 (1955)
189. Reed, E. A., and Scott, J. C., *Am. J. Physiol.*, **181,** 21–26 (1955)
190. Scott, J. C., and Reed, E. A., *Am. J. Physiol.*, **181,** 27–29 (1955)
191. Levy, M. N., Brind, S. H., and Brandlin, F. R., *Circulation Research*, **3,** 415–21 (1955)
192. Kisch, B., and Yuceoglu, Y. Z., *Exptl. Med. Surg.*, **13,** 378–84 (1955)
193. Enikeeva, S. L., *Fiziol. Zhur., U.S.S.R.*, **41,** 227–32 (1955)
194. Meulders, M., *Compt. rend. soc. biol.*, **149,** 1508–09 (1955)
195. Nardone, R. M., *Am. J. Physiol.*, **182,** 364–68 (1955)
196. Dawe, A. R., and Morrison, P. R., *Am. Heart J.*, **49,** 367–84 (1955)
197. Björck, G., and Johansson, B., *Acta Physiol. Scand.*, **34,** 257–72 (1955)
198. Siems, M. V., Horvath, S. M., Spurr, G. B., Hutt, B. K., and January, L. E., *Am. J. Physiol.*, **181,** 325–29 (1955)
199. Tysinger, D. S., Grace, J. T., and Gollan, F., *Am. Heart J.*, **50,** 816–22 (1955)
200. Covino, B. G., and Hegnauer, A. H., *Proc. Soc. Exptl. Biol. Med.*, **89,** 659–62 (1955)
201. Covino, B. G., and Hegnauer, A. H., *Am. J. Physiol.*, **181,** 553–58 (1955)
202. Covino, B. G., and Hegnauer, A. H., *Circulation Research*, **3,** 575–80 (1955)
203. Cookson, B. A., and DiPalma, J. R., *Am. J. Physiol.*, **182,** 447–53 (1955)
204. Montini, T., and Paoletti, G., *Arch. fisiol.*, **55,** 218–29 (1955)
205. Montini, T., and Paoletti, G., *Arch. fisiol.*, **55,** 230–42 (1955)
206. Hollander, P. B., and Webb, J. L., *Circulation Research*, **3,** 604–12 (1955)
207. Marshall, J., and Vaughan Williams, E. M., *J. Physiol. (London)*, **128,** 4–5P, (1955)
208. McCrory, C. B., and Virtue, R. W., *Proc. Soc. Exptl. Biol. Med.*, **90,** 327–29 (1955)
209. Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A., and Bing, R. J., *Ann. Surg.*, **139,** 275–81 (1954)
210. Badeer, H., *Circulation Research*, **3,** 28–31 (1955)
211. Badeer, H., *Am. J. Physiol.*, **183,** 119–20 (1955)
212. Sabiston, D. C., Theilen, E. O., and Gregg, D. E., *Surgery*, **38,** 498–505 (1955)
213. Wood, E. H., Bowers, D., Shepherd, J. T., and Fox, I. J., *J. Appl. Physiol.*, **7,** 621–28 (1955)
214. Hubay, C. A., Brecher, G. A., and Clement, F. L., *Surgery*, **38,** 215–27 (1955)
215. Howard, A. R., Hamilton, W. F., and Dow, P., *Am. J. Physiol.*, **175,** 173–77 (1953)

216. Vidt, D. G., Hanusek, G., Schieve, J. F., Hall, H. B., and Sapirstein, L. A., *Am. J. Physiol.*, **181**, 337–40 (1955)
217. Fowler, N. O., and Mannix, E. P., *J. Clin. Invest.*, **34**, 1242–46 (1955)
218. Huff, R. L., Feller, D. D., Judd, O. J., and Bogardus, G. M., *Circulation Research*, **3**, 564–69 (1955)
219. Dow, P., *J. Appl. Physiol.*, **7**, 399–408 (1955)
220. Shepherd, J. T., Bowers, D., and Wood, E. H., *J. Appl. Physiol.*, **7**, 629–38 (1955)
221. Hendricks, C. H., Quilligan, E. J., Sapirstein, L. A., Pultz, A. J., and Mandel, M. J., *Am. J. Med. Sci.*, **230**, 648–56 (1955)
222. Lacy, W. W., Ugaz, C., and Newman, E. V., *Circulation Research*, **3**, 570–74 (1955)
223. Rothe, C. F., and Sapirstein, L. A., *Am. Heart J.*, **48**, 141–45 (1954)
224. Falholt, W., and Kaiser, E., *Circulation Research*, **3**, 469–73 (1955)
225. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12**, 577–87 (1955)
226. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12**, 845–57 (1955)
227. Talbot, S. A., and Harrison, W. K., Jr., *Circulation*, **12**, 1022–33 (1955)
228. Tobin, M., Edson, J. N., Dickes, R., Flamm, G. H., and Deutsch, L., *Circulation*, **12**, 108–13 (1955)
229. Starr, I., *J. Appl. Physiol.*, **8**, 315–29 (1955)
230. Grandell, F. M., *Proc. Soc. Exptl. Biol. Med.*, **88**, 499–501 (1955)
231. De Simone, G., Cucci, C. E., and Maselli, F., *Arch. fisiol.*, **54**, 6–16 (1954)
232. Morris, G. L., and Braunstein, J. R., *Circulation*, **12**, 432–38 (1955)
233. Frederick, W. H., Thomas, H. D., Knowles, J. L., Tucker, W. T., and Eddleman, E. E., Jr., *Am. Heart J.*, **50**, 416–23 (1955)
234. Thomas, H. D., Frederick, W. H., Knowles, J. L., Reeves, T. J., Pappas, R., and Eddleman, E. E., Jr., *Am. Heart J.*, **50**, 424–34 (1955)
235. Remington, J. W., *Minnesota Med.*, **37**, 105–10 (1954)
236. Ronninger, R., *Arch. Kreislaufforsch.*, **22**, 332–73 (1955)
237. Giulio, L., *Arch. fisiol.*, **55**, 121–34 (1955)
238. Sarnoff, S. J., *Physiol. Revs.*, **35**, 107–22 (1955)
239. Berglund, E., *Acta Physiol. Scand.*, **33**, Suppl., 119 (1955)
240. Price, H. L., and Helrich, M., *J. Pharmacol. Exptl. Therap.*, **115**, 119–205 (1955)
241. Rushmer, R. F., *Circulation Research*, **3**, 639–44 (1955)
242. Bayliss, L. E., *J. Physiol. (London)*, **127**, 358–79 (1955)
243. Klepzig, H., *Arch. Kreislaufforsch.*, **23**, 96–161 (1955)
244. Björk, V. O., and Malmström, G., *Am. Heart J.*, **50**, 742–48 (1955)
245. Salisbury, P. F., *Circulation Research*, **3**, 633–38 (1955)
246. Hild, R., and Sick, L., *Z. biol.*, **107**, 51–66 (1954)
247. Berglund, E., Sarnoff, S. J., and Isaacs, J. P., *Circulation Research*, **3**, 133–39 (1955)
248. Isaacs, J. P., Berglund, E., and Sarnoff, S. J., *Am. Heart J.*, **48**, 66–76 (1954)
249. Cotten, M. deV., and Pincus, S., *J. Pharmacol. Exptl. Therap.*, **114**, 110–18 (1955)
250. Hilton, J. G., *Am. J. Physiol.*, **180**, 371–74 (1955)
251. Hild, R., and Herz, G., *Z. biol.*, **108**, 42–52 (1955)
252. Herz, G., *Z. biol.*, **108**, 111–20 (1955)
253. Burn, J. H., Vaughan Williams, E. M., and Walker, J. M., *Brit. Med. J.*, **1**, 574–76 (1955)

254. Harvey, R. M., Ferrer, M. I., Richards, D. W., and Cournand, M., *Circulation*, **12**, 507–19 (1955)
255. Storstein, O., and Tveten, H., *Scand. J. Clin. Lab. Invest.*, **7**, 167–72 (1955).
256. Starzl, T. A., Gaertner, R. A., and Baker, R., *Circulation*, **12**, 82–89 (1955)
257. Starzl, T. E., and Gaertner, R. A., *Circulation*, **12**, 259–70 (1955)
258. Starzl, T. E., Gaertner, R. A., and Webb, R. C., Jr., *Circulation*, **11**, 952–62 (1955)
259. Guyton, A. C., Lindsey, A. W., and Kaufman, B. N., *Am. J. Physiol.*, **180**, 463–68 (1955)
260. Freis, E. D., Broida, H. P., Hufnagel, C. A., and Rose, J. C., *Am. J. Physiol.*, **182**, 191–96 (1955)
261. Rose, J. C., Freis, E. D., Hufnagel, C. A., and Massullo, E. A., *Am. J. Physiol.*, **182**, 197–202 (1955)
262. Sunahara, F. A., Hatcher, J. D., Beck, L., and Gowdey, C. W., *Can. J. Biochem. Physiol.*, **33**, 349–60 (1955)
263. Gowdey, C. W., *Ontario Med. Rev.*, 1, (October 1954)
264. Gowdey, C. W., Hatcher, J. D., and Sunahara, F. A., *Can. J. Biochem. Physiol.*, **32**, 282–92 (1954)
265. Gowdey, C. W., and Young, I. E., *Can. J. Biochem. Physiol.*, **32**, 559–66 (1954)
266. Ferguson, T. B., Gregg, D. E., and Shadle, O. W., *Circulation Research*, **2**, 565–72 (1954)
267. Donald, K. W., Bishop, J. M., Cumming, G., and Wade, O. L., *Clin. Sci.*, **14**, 37–73 (1955)
268. Freedman, M. E., Snider, G. L., Brostoff, P., Kimelblot, S., and Katz, L. N., *J. Appl. Physiol.*, **8**, 37–47 (1955)
269. Asmussen, E., and Nielsen, M., *Physiol. Revs.*, **35**, 778–800 (1955)
270. Poppi, A., Barbieri, L. L., Martinelli, M., and Marini, M., *Cardiologia*, **26**, 173–82 (1955)
271. Theilen, E. O., Gregg, D. E., and Rotta, A., *Circulation*, **12**, 383–90 (1955)
272. Kokas, E., Miczban, I., and Toro, I., *Acta Physiol. Acad. Sci. Hung.*, **7**, 409–20 (1955)
273. Luisada, A. A., and Diamond, I., *Am. J. Physiol.*, **181**, 347–51 (1955)
274. Leüsen, I., Demeester, G., and DeWitte, J., *Arch. intern. pharmacodynamie*, **102**, 153–61 (1955)
275. Fawaz, G., *Proc. Soc. Exptl. Biol. Med.*, **88**, 654–56 (1955)
276. Dörner, J., *Arch. exptl. Pathol. Pharmakol.*, **226**, 152–62 (1955)
277. Gruhzit, C. C., and Farah, A., *J. Pharmacol. Exptl. Therap.*, **114**, 335 (1955)
278. Rothlin, E., Taeschler, M., and Cerletti, A., *Circulation Research*, **3**, 32–38 (1955)
279. Berman, D. A., and Saunders, P. R., *Circulation Research*, **3**, 559–63 (1955)
280. Garb, S., and Scriabine, A., *Am. J. Physiol.*, **180**, 101–2 (1955)
281. Garb, S., Penna, M., and Scriabine, A., *Am. J. Physiol.*, **180**, 103–6 (1955)
282. Chevillard, L., and Guerin, J., *Compt. rend. soc. biol.*, **149**, 235–38 (1955)
283. Alella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N., *Am. J. Physiol.*, **183**, 570–82 (1955)
284. Katz, A. M., Katz, L. N., and Williams, F. L., *Am. J. Physiol.*, **180**, 392–402 (1955)
285. Case, R. B., Berglund, E., and Sarnoff, S. J., *Am. J. Med.*, **18**, 397–405 (1955)
286. Katz, L. N., Katz, A. M., and Williams, F. L., *Am. J. Physiol.*, **181**, 539–49 (1955)

287. Harris, P., and Summerhayes, J. L. V., *Brit. Heart J.*, **17**, 453–58 (1955)
288. Case, R. B., Berglund, E., and Sarnoff, S. J., *Circulation Research*, **2**, 319–25 (1954)
289. Lasker, N., Sherrod, T. R., and Killam, K. F., *J. Pharmacol. Exptl. Therap.*, **113**, 414–420 (1955)
290. Hockerts, T., and Mülke, G., *Cardiologia*, **26**, 34–41 (1955)
291. Rowe, G. G., Huston, J. H., Maxwell, G. M., Weinstein, A. B., Tuchman, H., and Crumpton, C. W., *J. Clin. Invest.*, **34**, 696–99 (1955)
292. Arnulf, G., and Benichoux, R., *Arch. maladies coeur et vaisseaux*, **48**, 185–89 (1955)
293. Meesmann, W., and Schmier, J., *Z. Kreislaufforsch.*, **44**, 304–10 (1955)
294. Meesmann, W., and Schmier, J., *Pflügers Arch. ges. Physiol.*, **261**, 41–47 (1955)
295. Meesman, W., and Schmier, J., *Pflügers Arch. ges. Physiol.*, **261**, 48–60 (1955)
296. Lemley-Stone, J., Merrill, J. M., Grace, J. T., and Meneely, G. R., *Am. J. Physiol.*, **183**, 555–58 (1955)
297. LaDue, J. S., and Wroblewski, F., *Circulation*, **11**, 871–77 (1955)
298. Agress, C. M., Jacobs, H. I., Glassner, H. G., Lederer, M. E., Clark, W. G., Wroblewski, F., Karmea, A., and LaDue, J., *Circulation* **11**, 711–13 (1955)
299. Nydick, I., Wroblewski, F., and LaDue, J. S., *Circulation*, **12**, 161–68 (1955)
300. Linko, E., and Waris, E., *Scand. J. Clin. Lab. Invest.*, **7**, 135 (1955)
301. Linko, E., and Waris, E., *Scand. J. Clin. Lab. Invest.*, **7**, 141 (1955)
302. Eskola, O., Koskelo, P., and Halonen, P. I., *Am. Heart J.*, **49**, 258–61 (1955)
303. Fabre, H., and Linquette, Y., *Arch. maladies coeur et vaisseaux*, **48**, 669–72 (1955)
304. Eckstein, R. W., *Circulation Research*, **2**, 460–65 (1954)
305. Eckstein, R. W., *Circulation Research*, **3**, 306–10 (1955)
306. Temesvári, A., *Cardiologia*, **26**, 306–15 (1955)
307. Milch, E., Zimdahl, W. T., Egan, R. W., Hsia, T. W., Anderson, A. A., and David, J., *Am. Heart J.*, **50**, 483–91 (1955)
308. Struppler, A., *Med. Monatsschr.*, **3**, 155–59 (1955)
309. Struppler, A., *Z. biol.*, **108**, 58–64 (1955)
310. Struppler, A., *Z. biol.*, **107**, 416–28 (1955)
311. Wartman, W. B., Campbell, L. A., and Craig, R. L., *Circulation Research*, **3**, 496–500 (1955)
312. Hepper, N. G., Pruitt, R. D., Donald, D. E., and Edwards, J., *Circulation*, **11**, 742–48 (1955)
313. Teng, H. C., and Heyer, H. E., *Am. Heart J.*, **49**, 9–20 (1955)
314. Peel, A. A. F., *Brit. Heart J.*, **17**, 319–26 (1955)
315. Vague, J., Jouve, A., and Teitelbaum, M., *Arch. maladies coeur et vaisseaux*, **48**, 377–87 (1955)
316. Dawes, G. S., Mott, J. C., and Widdicombe, J. G., *J. Physiol. (London)*, **128**, 384–95 (1955)
317. Dawes, G. S., Mott, J. C., and Widdicombe, J. G., *J. Physiol. (London)*, **128**, 344–60 (1955)
318. Dawes, G. S., Mott, J. C., and Widdicombe, J. G., *J. Physiol. (London)*, **128**, 361–83 (1955)
319. Eldridge, F. L., and Hultgren, H. N., *J. Clin. Invest.*, **34**, 987–96 (1955)
320. Prec, K. T., and Cassels, D. E., *Circulation*, **11**, 789–98 (1955)

321. Born, G. V. R., Dawes, G. S., and Mott, J. C., *J. Physiol. (London)*, **130,** 191–212 (1955)
322. Hudson, R., *Brit. Heart J.*, **17,** 489–95 (1955)
323. Shaffer, A. B., Silber, E. N., and Katz, L. N., *Circulation*, **10,** 527–35 (1954)
324. Coelho, E., Borges, S., Padua, F., Nunes, A., Barata, M. I., Maltez, J., Pereira, S., and Duarte, C. A., *Cardiologia*, **26,** 1–20 (1955)
325. Müller, O., and Shillingford, J., *Brit. Heart J.*, **17,** 163–68 (1955)
326. Varnauskas, E., *Scand. J. Clin. Lab. Invest.*, **7,** Suppl., 17, 1–117 (1955)
327. Rose, J. C., Cosimano, S. J., Hufnagel, C. A., and Massullo, E. A., *J. Clin. Invest.*, **34,** 1625–31 (1955)
328. Hendricks, C. H., and Quilligan, E. J., *Circulation Research*, **3,** 506–09 (1955)
329. Brandfonbrener, M., Landowne, M., and Shock, N. W., *Circulation*, **12,** 557–66 (1955)
330. Landowne, M., Brandfonbrener, M., and Shock, N. W., *Circulation*, **12,** 567–76 (1955)
331. Fieldman, E. J., Ridley, R. W., and Wood, E. H., *Anesthesiology*, **16,** 473–89 (1955)
332. Price, H. L., and Helrich, M., *J. Pharmacol. Exptl. Therap.*, **115,** 206–16 (1955)
333. Boniface, K. J., Brown, J. M., and Kronen, P. S., *J. Pharmacol. Exptl. Therap.*, **113,** 64–71 (1955)
334. Bubnoff, M. von, Krieg, J., and Amiri, H., *Arch. exptl. Pathol. Pharmakol.*, **227,** 111–22 (1955)
335. Greisheimer, E. M., Ellis, D. W., Stewart, G., Makarenko, L., Thompson, K. T., and Oleksyshyn, M., *Am. J. Physiol.*, **182,** 145–47 (1955)
336. LaBarre, J., and Garrett, J., *Arch. intern. pharmacodynamie*, **100,** 418–24 (1955)
337. Broustet, P., Castaing, R., Bricaud, H., and Cottin, D., *Arch. maladies coeur et vaisseaux*, **48,** 859–71 (1955)
338. Gammill, J. F., Applegarth, J. J., Reed, C. E., Fernald, G. D., and Antenucci, A. J., *Ann. Internal Med.*, **43,** 100–19 (1955)
339. Bernath, J., Guillemot, R., Samuel, P., and de Balsac, R. H., *Am. Heart J.*, **50,** 112–28 (1955)
340. Davis, J. D., Hyatt, R. E., and Howell, D. S., *Circulation Research*, **3,** 252–258 (1955)
341. Davis, J. D., Howell, D. S., and Hyatt, R. E., *Circulation Research*, **3,** 259–263 (1955)
342. Meesmann, W., and Schmier, J., *Arch. exptl. Pathol. Pharmakol.*, **227,** 265–274 (1955)
343. Meesmann, W., and Schmier, J., *Pflügers Arch. ges. Physiol.*, **261,** 495–506 (1955)
344. McMillan, I. K. R., *Brit. Heart J.*, **17,** 56–62 (1955)
345. Harris, P., *Brit. Heart J.*, **17,** 173–82 (1955)
346. Friese, G., *Arch. Kreislaufforsch.*, **22,** 288 (1955)
347. Nylin, G., *Am. Heart J.*, **49,** 803–22 (1955)
348. Hackel, D. B., and Goodale, W. T., *Circulation*, **11,** 628–34 (1955)
349. McKusick, V. A., Webb, G. N., Humphries, J. O'N., and Reid, J. A., *Circulation*, **11,** 849–70 (1955)
350. McKusick, V. A., Kline, E. W., and Webb, G. N., *Am. Heart. J.*, **49,** 911–33 (1955)

351. McKusick, V. A., Webb, G. N., and Vescia, F. G., *Arch. maladies coeur et vaisseaux*, **48**, 504–11 (1955)
352. Rodbard, S., Mendelson, C. E., and Elisberg, E. I., *Cardiologia*, **27**, 144–153 (1955)
353. Dock, W., Grandell, F., and Taubman, F., *Am. Heart J.*, **50**, 449–64 (1955)
354. King, J. T., Lee, Y. C. P., and Visscher, M. B , *J. Nutrition*, **57**, 111–20 (1955)
355. Tourniaire, A., Fournie, G., Blum, J., and Semet, J., *Arch. maladies coeur et vaisseaux*, **48**, 738–57 (1955)
356. McAllen, P. M., *Brit. Heart J.*, **17**, 5–14 (1955)
357. Meesman, W., and Schmier, J., *Pflügers Arch. ges. Physiol.*, **261**, 32–40 (1955)
358. Hildes, J. A., Schaberg, A., and Alcock, A. J. W., *Circulation*, **12**, 986–93 (1955)
359. Busch, W., *Arch. Kreislaufforsch.*, **22**, 267–88 (1955)
360. Harvey, S. C., and Pieper, G. R., *J. Pharmacol. Exptl. Therap.*, **114**, 14–27 (1955)
361. Okita, J. T., Talso, P. J., Curry, J. H., Jr., Smith, F. D., Jr., and Geiling, E. M. K., *J. Pharmacol. Exptl. Therap.*, **113**, 376–82 (1955)
362. Carr, C. J., Bell, F. K., Rehak, M. J., and Krantz, J. C., Jr., *Proc. Soc. Exptl. Biol. Med.*, **89**, 184–86 (1955)
363. Price, K. C., Weiss, J. M., Hata, D., and Smith, J. R., *J. Exptl. Med.*, **101**, 687–93 (1955)
364. Becker, E. L., *Am. J. Physiol.*, **183**, 203–5 (1955)
365. Lev, M., and Lerner, R., *Circulation*, **12**, 176–84 (1955)
366. Prakash, R., *Indian Med. J.*, July, 164–65 (1954)
367. Prakash, R., *Proc. Zool. Soc. Bengal*, **7**, 27–36 (1954)
368. Prakash, R., *Proc. Nat. Inst. Sci. India*, **20**, 645–50 (1954)
369. Hellman, K., *Cardiologia*, **26**, 266–72 (1955)
370. Cavanaugh, M. W., *J. Exptl. Zool.*, **128**, 573–85 (1955)
371. Foxon, G. E. H., *Biol. Revs. Cambridge Phil. Soc.*, **30**, 196–228 (1955)
372. Ebert, J. D., Tolman, R. A., Mun, A. M., and Albright, J. F., *Ann. N. Y. Acad. Sci.*, **60**, 968–85 (1955)
373. Sippel, T. O., *J. Exptl. Zool.*, **126**, 205–21 (1954)
374. Sippel, T. O., *J. Exptl. Zool.*, **128**, 165–84 (1955)
375. Weidmann, S., *J. Physiol. (London)*, **127**, 213–24 (1955)
376. Hercus, V. M., McDowall, R. J. S., and Mendel, D., *J. Physiol. (London)*, **129**, 177–83 (1955)
377. McDowall, R. J. S., Munro, A. F., and Zayat, A. F., *J. Physiol. (London)*, **130**, 615–24 (1955)

VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM[1]

By Paul D. MacLean

Department of Physiology, Yale University School of Medicine, New Haven, Connecticut

Introduction

Some people think it will prove to be a tragedy for man that he cracked the atom before he cracked the brain. How, they ask, can he hope to harness the devastating powers of the atom before he has learned to understand, and thereby control, the potentially catastrophic forces within himself? Such an understanding will require more than psychological probing of the symbolic black box contained within the human cranium. It will depend also on a knowledge of brain mechanisms and what determines their giving rise to irrational behavior. In this regard, particular interest is attached to the role of primitive neural systems concerned with integrating visceral and somatic functions that ensure self-preservation and procreation. Investigative progress in this direction, however, promises to be hampered by the technical difficulties inherent in the study of the anatomy and physiology of finely myelinated and unmedullated fibers that make up such a large part of peripheral and central pathways. The growing realization of the importance of these fibers in visceral communication is indicated by the following informal remarks of Zotterman. Speaking of cardiovascular reflexes, he said:

> When we started working on them, we believed that the large afferent fibers from the right auricle were the sort of fibers subserving the real cardiac depressor effect, but we found out that they were not. The small delta fibers were the ones that were doing the trick. . . . The small fibers have been overlooked before. . . . I found out that the small fibers are contributing much more to our sensations than the large fibers. . . . The funny thing is that it is these tiny fibers which are giving us the emotions: their signalling is the basis of our emotional life (p. 204, ref. 1).

In view of the foregoing considerations, it is gratifying that such an experienced worker as Gasser has devoted especial attention in recent years to unmedullated fibers. His most recent study is concerned with the olfactory fila (3). He finds that physiologically they resemble s.C (sympathetic C) rather than d.r.C (dorsal root C) fibers. This is of interest in the light of the fact that olfaction is a visceroceptive as well as exteroceptive sense, and is so intimately involved in visceral functions.[2] Both Gasser (2, 3) and Hess (4) have made a number of striking anatomical observations on unmedullated fibers by means of electron microscopy. They have pointed out the

[1] The survey of literature pertaining to this review was concluded in July, 1956.

[2] The senses of smell and taste are usually considered elsewhere in this volume and will therefore not be reviewed here.

peculiar relation that several such fibers bear to a single Schwann cell and have discussed some of the physiological implications of their findings. Gasser states that electron microscopy is more essential for the visualization of olfactory nerve fibers than the "ordinary" unmedullated fibers. The former have a diameter of about 0.2μ and a conduction velocity (in the pike) of 0.2 m per sec.

The difficulties in investigating small fiber systems become greatly multiplied in passing from the peripheral to the central nervous system. Here the techniques of the anatomist have currently more to offer than those of the physiologist. Evans & Hamlyn have made a useful study on the respective advantages of the silver degeneration methods of Glees and of Nauta (5). Cowan & Powell (6) caution, however, against pseudodegenerative changes that may be seen with the Glees stain in certain parts of the brain and call into question previous reports of degeneration traced to parts of the septum and of the hypothalamus, particularly the dorsomedial and ventromedial nuclei.

The Limbic System

In recent years, there has been a growing interest in the role of the phylogenetically old cortex in viscerosomatic and emotional functions and in psychomotor epilepsy. The "old" cortex comprises the so-called archicortex and mesocortex. The archicortex and the greater part of the mesocortex are contained in the great limbic lobe which is found as a common denominator in the brains of all mammals. The "old" cortex and its associated nuclear structures constitute a functionally integrated system which may be appropriately referred to as the limbic system (7). The nuclear structures include the amygdaloid, septal, hypothalamic, anterior thalamic, and habenular nuclei and parts of the basal ganglia.

Many workers will welcome Kraft's translation into English of a number of Cajal's studies on limbic structures (8). Recent anatomical studies have dealt with secondary olfactory connections (9), the fornix system (10 to 13), and mammillary bodies (14). Droogleever Fortuyn (15) has given a general account of the anatomy of the limbic system. Of particular note is Nauta's confirmation (13) of a tract first described by Cajal and referred to as the cornual band of the tuber cinereum (8). This sizeable bundle from the fornix projects to the tuberal nuclei that sit astride the portal circulation of the pituitary.

Anand & Dua (16, 17) have stimulated the limbic frontotemporal cortex, anterior cingulate, hippocampus, and amygdala in a large number of cats and monkeys. Their study confirms a number of previously reported findings in regard to "eating automatisms," autonomic, and affective changes. In addition, they have found that stimulation of all the aforementioned structures, except the anterior cingulate, results in a moderate rise in the blood sugar level (18). A fall was found only upon stimulation of the anterior cingulate gyrus. They also report marked and varied changes in the volume and

in the free and total acid of the gastric contents, as well as inhibitory and excitatory effects on gastrointestinal motility (19).

Stamm (20) finds that female rats with bilateral ablations of the midline limbic cortex (cingulate) fail to nurse their young. Such lesions also interfere with nesting behavior. He concludes that the median cortex has a unique function in the integration of complex unlearned behavior patterns. Sexual manifestations have been noted in a few instances following chemical stimulation of the cortex bordering the posterior cingulate gyrus (21). According to Whitty (22), small bilateral lesions of the anterior cingulate in man have little effect on autonomic function save for transient urinary incontinence.

There is confirmation of Green and Arduini's findings that stimulation of the reticular formation evokes slow rhythmically recurring potentials in the hippocampus[3] (23, and see also ref. 21). More evidence has accumulated that various forms of sensory stimulation elicit similar changes (21, 23, 24). Observations have been made on changes in hippocampal activity during conditioning training (25, 26). Potentials similar to those elicited by olfactory stimuli are said to appear in the amygdalohippocampal region in man in association with emotional feelings or thoughts related to odors (27). Reserpine and ether have a similar distinctive effect on the electroencephalogram of the hippocampus (25). Radioautographic studies have shown that reserpine and barbiturate anesthesia appear to result in a depression of the high radioactivity ordinarily seen in the hippocampus following the administration of S^{35}-labeled *l*-methionine (25).

Further observations have been made on the seizure susceptibility of the hippocampus (24, 28, 29, 30) and other limbic structures (31, 32) as well as on the propagation of the induced discharges (24, 25, 28, 30, 32). Sawyer & Gernandt (33) have recorded seizures in the hippocampus and amygdala following repeated intracarotid injections of hypertonic saline. Olfactory stimulation is said to suppress spontaneous spiking activity in olfactory structures of the limbic system (34). Andy & Akert (28) have commented upon changes in respiration, arterial pressure, and pupillary size during hippocampal seizures. MacLean *et al.* (25) have found that propagating hippocampal afterdischarges abolish or markedly alter conditioned cardiac and respiratory changes. It is inferred that such seizures, being largely confined to limbic and perilimbic structures, bring about what must amount, in part, to a functional ablation of the limbic system.

Unitary responses have been recorded from the hippocampus (35, 36, 37) and the amygdala (38). As one might have been led to expect on the basis of previous findings, units have been found that respond to several forms of sensory stimulation (37, 38). Electrophysiological methods have been used to trace the connections of the hippocampus (39) and amygdala

[3] The greater part of the archicortex is folded into the hippocampus, a structure that has strong connections with the hypothalamus.

(40, 41). Incidental to these studies, striking post-tetanic potentiation was seen in the hippocampus, a finding that may prove to have important bearing on the function of this structure (39, 41). Gloor (40) concludes that fibers originating in the amygdala seem to belong mainly to the group of thinly myelinated and unmyelinated elements and that some of the properties of the amygdaloid projection system are best explained on the assumption that part of the neurones are comparable to autonomic elements of the C-fiber group (see introduction of this review).

Koikegami and co-workers (42, 43) have continued their systematic investigations of the amygdaloid complex. They have made the observation, highly significant if confirmed, that bilateral amygdaloidectomy in young puppies results in generalized atrophy of the endocrine glands (42). The work of Mason (44) provides evidence of a significant elevation of plasma 17-hydroxycorticosteroids following stimulation of the amygdala. Ovulation and uterine movements have also been observed as the result of such stimulation (43). Schreiner & Kling (45) have published further observations on the docility [see also Karll (46] and chronic hypersexuality that occur in animals following bilateral amygdaloidectomy. Bizarre sexual behavior and other manifestations of the Klüver-Bucy syndrome have been reported in man following bilateral temporal lobectomy including the amygdala and most of the hippocampus (47) [see also the work of Sawa *et al.* (48)]. Electrical stimulation has been carried out in the region of the amygdala in man (49, 50). Chapman *et al.* (50) recorded rises in the systolic arterial pressure as high as 80 mm. Hg.

Brady & Nauta (51) have described the effects of septal and habenular lesions on affective behavior in rats. Septal lesions commonly result in a partial attenuation of the conditioned emotional response, of which defecation is one of the manifestations. Habenular lesions result in a rapid extinction of this response.

Hypothalamus

A recent book by Harris (52) with a subsequent paper (53) on the neural control of the hypothalamus provides an excellent critical review of the work in this field. It also has the value of bringing together in one place a well illustrated account of the work of himself, Green, and others on the portal circulation of the pituitary. Benoit & Assenmacher (54) have made a very extensive, illustrated review of the hypothalamic control of gonadal function. Gloor (55) has written a clear and useful summary for English readers of Hess's work on the diencephalon. Gellhorn (56) has reviewed the recent work in his laboratory concerned with the neural mechanisms involved in Funkenstein's test (57 to 62). He points out that this test reveals that electroshock treatment results in clinical improvement only in patients who show a deficient sympathetic hypothalamic reactivity. On the basis of animal experimentation, he believes that the Mecholyl and norepinephrine tests may be used respectively as indicators of sympathetic and parasympathetic

excitability of the hypothalamus. The results of these studies also lead him to adhere to the view that a parasympathetic center exists in the anterior hypothalamus and a sympathetic center in the posterior part, and he concludes that the principle of reciprocal innervation seems to be valid for the hypothalamus. His claim that deficient sympathetic hypothalamic reactivity is a contributing factor in the psychoses is difficult to reconcile with the beneficial mechanism of action attributed to the so-called ataraxic or tranquilizing drugs. The action of reserpine and of chlorpromazine has been variously interpreted as having either an inhibiting or a direct depressing effect on the sympathetic centers of the hypothalamus. In regard to the central action of reserpine, the reader is referred to papers by Bein (63) and Schneider *et al.* (64, 65). Schneider postulates that reserpine inhibits the play of afferent impulses on the sympathetic centers of the hypothalamus (64). Other investigations concerned with this problem are cited in the references (25, 66, 67, 68). Communications dealing with the effects of tranquilizing and psychosomimetic drugs (and substances related to them) on visceral and other functions of the nervous system are appearing in such numbers that one foresees the day when a separate chapter will be devoted to this subject in the *Annual Review of Physiology*.

Studies have been made on the cytoarchitectonics (69) and angioarchitectonics (70) of the hypothalamus in man.

For indicating the organization of the rest of this section, the reader is asked for the moment to visualize the hypothalamus as a little sail boat with a keel. A dangling anchor below the prow would correspond to the optic chiasm; the lead and wooden parts of the keel, to the anterior and posterior pituitary, respectively; and the rudder, to the mammillary body. By starting at topdeck amidships and proceeding to the prow, back to keel, and then to the stern, one can achieve in some degree a parallel continuity in the consideration of structures and the presentation of subject matter.

Dorsal hypothalamus.—Andersson & McCann (71) have obtained further evidence in support of their postulated "drinking area" in the hypothalamus. Upon stimulation of the hypothalamus in goats, they found that the points eliciting drinking were located in the region of the dorsal hypothalamus between the columns of the fornix and the mammillothalamic tract. Stimulation of the anterior part of this region resulted also in milk ejection and antidiuresis. Complemental to this study, electrolytic lesions were made in various parts of the hypothalamus in dogs (72). Hypodipsia is said to have occurred in 6 of 15 animals when the lesions involved the so-called drinking area. (See also section on lateral hypothalamus.)

Preoptic region.—Maire & Patton (73) have extended the original observations made by Gamble and Patton on "preoptic pulmonary edema". It is now considered that midline preoptic lesions produce lung edema more consistently than laterally placed lesions. They present evidence that the condition results from release of the caudally lying sympathetic centers. Their experiments on the peripheral component of the mechanism lead them

to believe that the edema results from overloading of the pulmonary circuit as the result of splanchnic-mediated constriction of visceral venous reservoirs (74). Grossman & Wang (75), through the use of stimulation and lesion techniques, have localized neural elements in the septum pellucidum and the preoptic area that exert control over the urinary bladder. Katsuchi *et al.* (76) have elicited bladder responses from the preoptic region, as well as contractions of rectum and uterus and a fall in arterial pressure.

Supraoptic region.—Studies have been made on the time of appearance of neurosecretory material in the supraoptic region of the chick embryo (77, 78). The development of new histochemical techniques has provided the first histochemical evidence of the hypothalamic elaboration of posterior pituitary hormone in man and rat (79, 80). The intracarotid injection of epinephrine prevents the antidiuretic effect of a subsequent injection of acetylcholine (81). In the aforementioned study on the "drinking area," Andersson & McCann (71) found that electrical stimulation within the supraoptic region resulted in an inhibition of water diuresis and milk ejection; there was no polydipsia. Hagen (82) describes degenerated areas in the diencephalon and neurohypophysis in 13 cases of diabetes mellitus in man. Experimentally, severe shrinking of the nerve cells of the median part of the supraoptic nucleus of the dog was found following removal of the pancreas (82). Is it possible that these changes could be secondary to the chronic stimulus of dehydration, or are they to be correlated with the fall in the blood sugar level that is reported to result from stimulation of the medial part of the supraoptic and anterior and middle hypothalamic regions (83)? A study is reported on the blood sugar in individuals treated with hypothalamic extract (84).

Ventromedial nuclei.—Continued investigation on hypothalamic obesity leaves little doubt that lesions of the ventromedial nuclei are a determining factor in this condition (85 to 88). Goldthioglucose injections result in extensive, and apparently quite selective, damage of these nuclei and bring about the same manifestations that follow electrolytic lesions (88). The hypodipsia seen in obese hyperphagic animals is attributed by Montemurro & Stevenson (87) to "a dramatic increase in food consumption without any significant increase in water intake." In analyzing the influence of dietary factors, Teitelbaum (89) concludes that the obese hyperphagic animal shows a release from inhibitions insofar as it is hyperreactive to positive and negative stimulus qualities of the diet. In this same regard, Fuller & Jacoby (90) have drawn a parallel between genetically obese mice and rats with experimental hyperphagia.

Lateral hypothalamus.—Anand *et al.* (91) placed electrolytic lesions in different hypothalamic regions in 16 cats and 17 monkeys. Bilateral destruction of the lateral hypothalamus resulted in aphagia. In contrast, stimulation of the lateral hypothalamus brought about an increase in food intake (92). The results are interpreted as confirming the presence of a "feeding center" in the lateral hypothalamus that was first postulated by Anand & Brobeck on

the basis of findings in the rat. It is to be pointed out, however, that both lesions and stimulations in these experiments were in a postition to involve important neural pathways, including the medial forebrain bundle, and that the problem of controlling the role of extrahypothalamic mechanisms in the resulting aphagia will be difficult indeed. Reminiscent of an animal deprived of its forebrain, two of the monkeys reported would eat if food were placed in the mouth (91). Useful as such terms as "feeding center," "drinking area," etc., are for brevity of expression, they have the drawback of diverting attention from the functional relationship of the so-called centers with other parts of the brain.

Montemurro & Stevenson (87) report that small lesions in the lateral hypothalamic areas of rats produce "no significant increase in food intake, but a reduction in water intake." These and other findings lead them to infer that the hypothalamic area responsible for hypodipsia is situated "predominantly" in the same region as the "feeding center." Greer (93) reports a single case of a rat that showed "violent drinking activity" upon electrical stimulation of the lateral hypothalamus at the level of the lower dorsomedian nucleus. On the basis of electroencephalographic recordings from the hypothalamus, Brobeck *et al.* (94) suggest that amphetamine excites the medial portion of the hypothalamus which contains an inhibitory part of a "feeding center."

Neural control of anterior pituitary.—The reviews of Harris (52, 53) and of Benoit & Assenmacher (54) already referred to, and Chapter 4 of the volume on pituitary-adrenal relationships are recommended.

Piecing together our knowledge of the functions of the nervous system is somewhat like putting together a jig-saw puzzle with many missing pieces. For a long time, there has been missing what seems to be a pivotal cornerpiece in the hypothalamic pituitary region. Recently there has been considerable activity in trying to fit the posterior pituitary hormones into the picture of the neural control of the adenohypophysis. McCann and coworkers (95) have presented evidence that lesions which interrupt the supraopticohypophyseal tract and induce marked diabetes insipidus prevent the rise in blood ACTH that is ordinarily associated with various stresses (cf. 96, 109). In line with these findings are the observations indicating that the posterior pituitary hormones can activate the anterior pituitary to discharge ACTH (97, 98, 99). Guillemin & Hearn (100) attribute the activating capacity of commercial pitressin to a contaminant of vasopressin of probable hypothalamic origin. It should also be noted that commercial pitressin contains minute amounts of a histamine-like substance (101). From the results of experiments employing morphine as a blocking agent,[4] Briggs & Munson (102) conclude that the postulated hypothalamic neurohormone activating the adenohypophysis is not histamine, epi-

[4] There is evidence that morphine blocks pituitary activation through its action on the central nervous system (102, 103).

nephrine, or vasopressin. Porter & Jones (104) claim that blood from the hypophyseal portal vessels contains a substance which accelerates the release of ACTH. They believe the substance is either a large protein molecule or is bound to a large protein and is not identical with vasopressin (105). Guillemin & Rosenberg (106) report that hypothalamic tissue will activate the release of ACTH from the pituitary *in vitro*. Saffran & Schally (107) claim, however, that hypothalamic tissue alone is ineffective. They found that the greatest stimulation of ACTH-release occurs with posterior pituitary tissue plus norepinephrine and conclude that the posterior pituitary is probably involved in the response of the anterior pituitary-adrenocortical system to stress.

Experiments involving electrical stimulation (108) and the placement of lesions (109, 110) in the hypothalamus point to the median eminence as the most crucial part of the neural mechanism concerned with activating the release of ACTH. The ovaries also show arrested follicular growth when lesions are placed in this region (109; cf. 111 and 112). Reserpine results in castration-like changes in the genital organs of male and female rats, presumably as a consequence of its action on central neurohumoral mechanisms (113, 114). The time of administration of morphine has been shown to be an important consideration in studies on its inhibiting effect on the release of pituitary gonadotrophin in rodents (115). Beach *et al.* (116) have reported that electro-convulsive shock results in an increase in the mean frequency of ejaculations in male rats.

Von Euler & Holmgren (117) have observed that rabbits with pituitary grafts in the anterior chamber of the eye release thyroidal radioiodine at about the same rate as normal controls. These and other findings lead them to conclude that the feed-back control of thyroid secretion is not impaired by disconnecting the normal pathways between hypothalamus and anterior pituitary gland. They point out, however, that the setting of the feed-back system to an adequate level of circulating hormone seems impossible in the absence of the normal hypothalamohypophyseal connections. Other studies have been concerned with the effects of hypothalamic lesions on thyrotropin secretion by the pituitary (110, 118, 119). The area most vital in influencing the release of thyrotropin appears to be in and above the anterior part of the median eminence (110, 119). There is suggestive evidence that adrenal cortical hormones suppress the thyrotropin output of the anterior pituitary concomitantly with their inhibiting effect on the release of ACTH (120).

Posterior hypothalamus.—Stimulation of the posterior hypothalamus, as well as the lateral hypothalamus, results in a rise in the blood sugar level (83). A "fairly discrete pathway" involved in shivering has been traced from the posterior hypothalamus to the spinal cord (121). Anand (122) has drawn attention to the somnolence that occurs with lesions of the mammillary region and discusses the implications in regard to "the activating system of the cephalic brain stem." Lesions in the retromammillary region diminish or abolish the augmenting action of epinephrine on cortically

evoked movements and on the patellar reflex (123). The role of the hypothalamus and other parts of the central nervous system in regard to leucocytosis and phagocytosis has been investigated (124).

Neocortex

Auer (125) has studied the terminal degeneration in the diencephalon after ablation of the frontal cortex. The hypothalamus is characterized by terminal degeneration and degenerating fibers of passage in the medial forebrain bundle. Little degeneration is observed in the ventromedial, mammillary, and posterior hypothalamic nuclei. Gardner *et al.* (126) have confirmed the findings of previous workers that stimulation of the splanchnic nerves evokes potentials in somatic areas I and II, and ipsilateral II in the cat, and similarly conclude that these responses depend on the activation of fast-conducting fibers. They were, however, unable to evoke potentials in the monkey. They point out that the number of large myelinated fibers in the splanchnic of the monkey is sparse compared with the cat and suggest that this may account for their negative findings.

Electrocorticographic study has shown that anaphylaxis in the rat and guinea pig results in generalized "epileptic patterns of discharge" (127). Further observations have been made on the effect of epinephrine on the bioelectrical activity (128) and functions of the cortex. Intravenous epinephrine, and norepinephrine to a lesser degree, augment cortically evoked movements as well as the patellar reflex (123). Further observations have been made of the contrasting effects on arterial pressure of topical application of epinephrine to and electrical stimulation of the temporal cortex (129). Opposing effects of the anterior and posterior pituitary hormones on the "chronaxie" of cortex have been described (130). Thoracic sympathectomy results in a diminution of the rise of arterial pressure normally following stimulation of the motor and premotor cortex (131). Kojima (132) has studied the representation of various autonomic functions in the cerebral cortex. Stimulation of the frontal and parietal lobes is stated to result in an acceleration of respiration and a rise of arterial pressure. Klopper has found that after elimination of the influence of the spleen, one obtains a fall, rather than a rise, of the arterial pressure upon stimulation of the frontal and temporal areas (133). The pressor response to stimulation of the orbital cortex is unchanged. Kessler (134) has described skin temperature disturbances following postcentral and precentral cortical lesions. Beach *et al.* (135) have concluded that the changes in mating behavior in male cats following frontal lesions is attributable to the resulting motor impairment.

Reticular System, Midbrain, Pons, Medulla

Magoun (136) has reviewed the work of the Los Angeles school on stress mechanisms of the cephalic brainstem and has discussed its significance in regard to visceral functions and psychosomatic disorders. Papez (137, 138) has given accounts of the anatomical organization of the reticular system

that will be helpful to neurophysiologists. Rossi & Brodal (139) have found a projection of fibers from all parts of the cerebral cortex to the pontine and medullary reticular formation and point out that this could provide the anatomical substrate for cortical influences on somatomotor activity, respiration, and cardiovascular function. Previous neurophysiological studies have emphasized the convergence of somatic and visceral afferents on cells of the reticular formation. Limiting their study to reticular cells that could be influenced by surface-positive polarization of the anterior lobe of the cerebellum, Scheibel *et al.* (140) have found that single and repetitive stimuli to the vagus nerve were completely without effect on units activated by auditory and somatic stimuli. Grastyán *et al.* (141) have observed that conditioned alimentary and defensive reflexes can be facilitated or inhibited by stimulation of the hypothalamus and reticular formation and have noted the reciprocal effects of such stimulation on these reflexes.

In an extensive study Lindgren (142) has identified tectofugal vasodilator and vasoconstrictor pathways that are anatomically and functionally separate from vasomotor centers in the medulla, and has discussed their significance in regard to the influence of higher centers on the cardiovascular system. Tang & Ruch (143, 144) have investigated the effects of lesions at various levels of the neuraxis on the micturition reflex. They find an area between the transhypothalamic and superior collicular levels that has a facilitating effect on the micturition reflex, and another area between the supracollicular and intercollicular levels that has an inhibitory effect. Subcollicular transection or spinal transection completely abolish the reflex. Investigations on the effects of brain-stem lesions on metabolism and electrolyte balance have led to variable and inconclusive findings (145, 146).

Katsuki and coworkers have focused attention on the autonomic representation in the basilar part of the pons. In addition to their demonstration that this part of the brain participates in the regulation of respiration (147) and arterial pressure (148, 149), they have located a region in the ventromedial portion of the pons that exerts an inhibitory influence on intestinal movements by way of the splanchnic nerves (150).

Russell (151) has reviewed the literature and made an interesting comparative study on the locus coeruleus which is found as a conspicuous structure in all mammals. He proposes that this nucleus subserves a relay function in the cortical and subcortical facilitation of the central nervous system control over general bodily vegetative functions. On the basis of stimulation studies, Baxter & Olszewski (152) suggest that the cells of this nucleus form a major part of the so-called pneumotaxic center. It has also been suggested that the inferior olive which has been found to receive a rather massive projection from the periaqueductal gray plays an important role in the regulation of autonomic functions (153).

A recent study of the anatomy of the dorsal vagal nucleus indicates it is a nucleus of the mixed type, containing both motor and sensory elements (154). A number of investigations have been carried out on the respiratory

(155, 156), cardiovascular (157), and gastric functions (158, 159) of the medulla. Bell & Lawn have localized a "reticulo-ruminal center" which they believe may coordinate a chain of reflexes associated with rumination (158). A comparative anatomical study of the area postrema has given confirmatory evidence of the presence of nerve fibers in this structure (160). Whether or not these fibers bear an afferent or efferent relationship to the cells and blood vessels remains undetermined. Amols & Merritt (161) discuss the mechanism of action of chlorpromazine on the alleged chemoceptive trigger zone in the area postrema and on the reticular vomiting center.

Peripheral Autonomics: Neural Mechanisms

Using microelectrodes for intracellular recording, Tauc & Eccles have respectively studied the bioelectrical activity of individual ganglion cells in the mollusk (162, 163, 164) and the rabbit (165). In the rabbit, the resting potential of these cells (65 to 80 mv.) is in the range of that of mammalian motor neurones. The spike potential ranges from 70 to 96 mv. and has a duration of four to seven msec. Synaptic potentials, when uncomplicated by spike potentials, may reach 30 mv. and last 20 to 60 msec. The ganglion cells are capable of responding to repetitive stimulation of the preganglionic fibers at frequencies up to 100 per second. Tauc (162) concludes from his studies on the mollusk that there is a parallel between the bioelectrical properties of ganglionic nerve cells and unmyelinated fibers.

Oscarsson (166) has reinvestigated the functional organization of the two presynaptic systems of the colonic nerve in the inferior mesenteric ganglion of the cat and presents evidence to show that the antagonistic effects obtained upon stimulating the two systems are the result of convergence and occlusion. Downmann (167) has made an extensive bioelectrical study on the reflex arcs involved in skeletal muscle reflexes mediated by the splanchnic and intercostal nerves.

Further work has been done on the effects of anesthesia on the metabolism and conduction of autonomic ganglia and fibers (168, 169). Edwards & Larrabee (168) conclude that anesthetics do not have a single site of action on nerve metabolism and function, and that there is no simple correlation between the observed metabolic and functional effects. Volatile anesthetics increase the sensitivity of baroreceptors (170). Ganglia infected with pseudorabies virus show spontaneous neuronal activity that is attributed to a hyperexcitability of the presynaptic fiber terminations caused by the infection (171). Extracts have been obtained from brain tissue that interfere with neural transmission in some autonomic ganglia (172, 173). The isolated hypogastric nerve-uterus preparation (174) and isolated vagus nerve-heart preparation (175) have been used to test the effects of chemical agents on neural transmission. A method is described for testing the effects of acetylcholine and other drugs on the superior cervical ganglion *in vitro* (176).

Acetylcholine.—Emmelin & MacIntosh (177) find that the amounts of acetylcholine (ACh) liberated by preganglionic volleys are enough to justify

the belief that ACh acts as a synaptic transmitter. Temperatures from 20 to 40° C. are without appreciable effect on the liberation of ACh, but there is a significant reduction in the range of 10 to 20° C. (178). So long as the perfusion fluid contains 30 per cent of normal sodium concentration, no change in the amount of ACh released on preganglionic stimulation can be detected (179). With further lowering of the sodium concentration, the output of ACh is decreased abruptly. The liberation of ACh by potassium is independent of the presence of sodium. Observations have been made on the differential effect of anticholinesterases on the respective excitatory actions of ACh and of potassium (180).

Epinephrine and norepinephrine.—Sympathetic stimulation liberates an epinephrine-like substance in the skin of the frog that lowers the threshold and slows the adaptation of tactile receptors (181). Sympathetic stimulation also increases (*a*) the twitch peak tension of fatigued frogs' muscles and (*b*) the tension produced by the unfatigued slow skeletal muscle fibers in response to excitation of the small motor nerve fibers (182). In curare preparations, sympathetic stimulation, epinephrine, and norepinephrine increase the amplitude of the end-plate potential, but do not affect significantly the resting potential. Norepinephrine sensitizes the motor end-plate to acetylcholine. In the dog there are indications that epinephrine increases synaptic transmission in the celiac ganglia and neuroglandular transmission in the adrenal glands, and also augments the effects of locally applied acetylcholine (183). These findings stand in contrast to the report that epinephrine depresses synaptic transmission in the superior cervical ganglion of cat (184). Further experiments are described that suggest that monoamine oxidase plays a minor role in the degradation of epinephrine and norepinephrine *in vivo* (185). Evidence is presented that the adrenal glands contain a substance that destroys the chemical mediator liberated by adrenergic nerves (186).

Sensitization to acetylcholine and epinephrine.—Strömblad (187 to 192) has prosecuted investigation on the fundamental problem of explaining the sensitization to acetylcholine and epinephrine that follows denervation. In the salivary glands, he finds that postganglionic denervation results in a 60 per cent reduction of the enzyme destroying acetylcholine and that preganglionic denervation is followed by a 30 per cent reduction (187). Curiously enough, chronic treatment with pilocarpine protects against denervation sensitivity to acetylcholine and epinephrine whereas chronic administration of an atropine-like drug to normal preparations results in a picture of denervation sensitivity (188). There are intimations from these and other of his studies in progress that the reduction of cholinesterase activity in the salivary gland cannot entirely explain the phenomenon of acetylcholine sensitization. On the basis of their experiments, Perry & Reinert (193) suggest that the effect of denervation is attributable to a fall in the intracellular potassium concentration of ganglion cells and a consequent inhibition of oxidative metabolism.

Brain.—Bilateral removal of the superior cervical or stellate ganglia in ferrets more than doubles the time required for light-induced estrus in controls (194). Infiltration of the superior cervical ganglia in man with novocaine is said to interrupt diuresis as the result of provoking an increase of the antidiuretic hormone in the blood (195, 196). Cocainization or extirpation of the cervical sympathetic ganglia or the administration of epinephrine increases the permeability of the blood-brain barrier (197). Upon reviewing 533 cases collected from the literature, de Takats (198) finds that cervical sympathetic block was of immediate benefit in 65 per cent of patients with apoplexy. Over half of his own cases were helped by this emergency treatment (198).

Eye.—In an investigation employing atropine and physostigmine, Cervoni *et al.* (199) find no support for the hypothesis that there is a cholinergic mechanism in the innervation of the nictitating membrane of the cat. On the basis of observations on animals with unilateral superior cervical ganglionectomy, it is suggested that the mechanism involved in ocular accommodation may be partially vascular in nature (200).

Salivary glands.—Emmelin (201) has failed to find justification for the view that in the submaxillary gland of the cat there are groups of secretory cells that are respectively innervated by parasympathetic and sympathetic fibers. On the contrary, he reports that the results of his experiments are in agreement with the conclusions of Langenskiöld that all secretory cells in the submaxillary gland that are innervated by the sympathetic nerves are also innervated by the chorda tympani. By the use of various sympathetic blocking agents, he believes he is able to separate the secretory and vasoconstrictor effects of sympathetic stimulation (202).

Lactation.—By making various nerve sections in the periphery and in the neuraxis, Eayrs & Baddeley (203) have attempted to identify the nervous pathways involved in the maintenance of lactation by the act of suckling. It is inferred that the nerves mediating the suckling stimulus enter the central nervous system by the dorsal roots and ascend in the spinal cord deep in the lateral funiculus of the same side. The pathway to the diencephalon appears to be either indirect or unmyelinated, and widely dispersed throughout the reticular formation.

Respiration.—Wyss (204) and Meulders (205) have studied, respectively, the periodic relationship of action potentials in the efferent vagus and sympathetic nerves to those in the phrenic, and have speculated about the nature of the central controlling mechanisms. In recording from the carotid sinus nerve, Witzleb *et al.* (206) have found that small decreases in oxygen pressure in the range of 115 to 80 mm. Hg cause a considerable increase of action potentials; little further change was noted at lower pressures. Serotonin (5-hydroxytryptamine) has a pronounced stimulating effect on the carotid chemoreceptors (207). The associated change in respiration is presumed to contribute to the pressor response elicited by intravenous injection

of this substance. Denervation of the chemoreceptors in the rabbit results in an increase of the reticulocyte count (208). The physiology of a primary chemoreceptor unit has been described (209). Evidence is given of the existence of a pulmonary depressor reflex (210). Of practical import for the anesthesiologist is the finding that atropine increases the respiratory dead space (211).

Circulation.—Developments in regard to autonomic regulation of the circulation, including the extensive work on baroreceptor physiology, will be considered elsewhere in this volume. In view, however, of the emphasis placed on small fiber systems in the introduction of this review, attention is called here to the studies by Douglas and co-workers (212, 213). They have observed that the aortic nerve contains a large group of small unmyelinated fibers with powerful reflex depressor activity, and have shown how frequency of stimulation determines the activation of various fiber populations in this and the carotid sinus nerve, as well as the type of reflex that is obtained.

Gastrointestinal tract.—Kuntz & Napolitano (214) have given an anatomical description of neuroeffector formations in gastrointestinal muscle. Several studies have respectively shown the important role of the vagus in conveying "distension stimuli" (215 to 219), in regulating the amount of food and water consumed (219), in reticuloruminal reflexes (216, 217, 218), and in the gastric secretion of acid (220). Observations have been made on the functional restitutions that occur with vagosympathetic and vagosplanchnic anastomoses (221, 222). Alimentary osmoreceptor mechanisms in man have been investigated (223).

Pacemaking mechanisms in the upper bowel have been studied in relation to the slow potentials that are recorded electrically (224). A report has been given of the mutual interaction of the vagus and pelvic nerves on the large bowel (225). Stimulation of the parasympathetic and sympathetic outflows to the colon of the rabbit *in vitro* has brought to light a number of findings that may help to explain contradictory results in previous investigations (226). In this preparation, Garry & Gillespie have found that stimulation of the pelvic nerves always causes contraction and stimulation of the lumbar outflow inhibition. Maximum contraction is obtained with slow frequencies of stimulation, maximum inhibition with high frequencies. Simultaneous stimulation of both outflows with low frequencies elicits only a motor response; stimulation with high frequencies, only inhibition. Observations on the isolated gut suggest the presence in the intestine of ganglionic cells that give origin to postganglionic adrenergic fibers (227).

Urinary bladder.—Iggo (217) has recorded from single afferent fibers in the pelvic plexus during passive distension and active contraction of the urinary bladder. There is evidence that the discharge under isotonic and isometric recording conditions is related to intravesical pressure and that the receptors in the bladder are slowly adapting. He concludes that the bladder receptors are tension recorders "in series" with the muscle fibers. In an extensive investigation involving severance of peripheral nervous pathways

and transection at various levels of the neuraxis, as well as other manipulations, Tang & Ruch (144) have concluded that bladder tonus, in contradistinction to the micturition reflex, is nonneural in nature. Two clinical studies refer to the incidence and duration of disturbances in bladder function following cordotomy (228) and spinal cord injuries (229).

LITERATURE CITED

1. *Nerve Impulse. Transactions of the Fourth Conference, March 4, 5, and 6*, 1953. (Nachmansohn, D., Ed., Josiah Macy, Jr. Foundation, 224 pp. New York, N. Y., 1954)
2. Gasser, H. S., *J. Gen. Physiol.*, **38**, 709–28 (1955)
3. Gasser, H. S., *J. Gen. Physiol.*, **39**, 473–96 (1956)
4. Hess, A., *Proc. Roy. Soc. (London)*, **144**, 496–506 (1956)
5. Evans, D. H. L., and Hamlyn, L. H., *J. Anat.*, **90**, 193–203 (1956)
6. Cowan, W. M., and Powell, T. P. S., *J. Anat.*, **90**, 188–92 (1952)
7. MacLean, P. D., *Electroencephalog. Clin. Neurophysiol.*, **4**, 407–18 (1956)
8. Ramón y Cajal, S., *Studies on the Cerebral Cortex [Limbic Structures]*. (Trans. from Spanish by L. M. Kraft. Lloyd-Luke, Ltd., London, and The Year Book Publishers, Inc., Chicago, Ill., 179 pp. 1955)
9. Gamble, H. J., *J. Anat.*, **90**, 15–28 (1956)
10. Daitz, H. M., and Powell, T. P. S., *J. Neurol. Neurosurg. Psychiat.*, **17**, 75–82 (1954)
11. McLardy, T., *J. Comp. Neurol.*, **103**, 305–25 (1955)
12. McLardy, T., *J. Comp. Neurol.*, **103**, 327–43 (1955)
13. Nauta, W. J. H., *J. Comp. Neurol.*, **104**, 247–71 (1956)
14. Guillery, R. W., *J. Anat.*, **89**, 19–32 (1955)
15. Droogleever Fortuyn, J., *Electroencephalog. Clin. Neurophysiol.*, **4**, Suppl., 149–62 (1955)
16. Anand, B. K., and Dua, S., *Indian J. Med. Res.*, **44**, 107–19, (1956)
17. Anand, B. K., and Dua, S., *Science*, **122**, 1139 (1955)
18. Anand, B. K., and Dua, S., *Indian J. Med. Res.*, **44**, 121–24 (1956)
19. Anand, B. K., and Dua, S., *Indian J. Med., Res.* **44**, 125–30 (1956)
20. Stamm, J. S., *J. Comp. Physiol. Psychol.*, **48**, 347–56 (1955)
21. MacLean, P. D., *Psychosomat. Med.*, **17**, 355–66 (1955)
22. Whitty, C. W. M., *Proc. Roy. Soc. Med.*, **48**, 463–69 (1955)
23. Passouant, P., Cadilhac, J., and Passouant-Fontaine, T., *J. physiol. path. gén.*, **47**, 715–18 (1955)
24. Liberson, W. T., and Akert, K., *Electroencephalog. Clin. Neurophysiol.*, **7**, 221–22 (1955)
25. MacLean, P. D., Flanigan, S., Flynn, J. P., Kim, C., and Stevens, J. R., *Yale J. Biol. Med.*, **28**, 380–95 (1955/56)
26. Galambos, R., Sheatz, G., and Vernier, V. G., *Science*, **123**, 376–77 (1956)
27. Lesse, H., Heath, R. G. Mickle, W. A., Monroe, R. R., and Miller, W. H., *J. Nervous Mental Disease*, **122**, 433–40 (1955)
28. Andy, O. J., and Akert, K., *J. Neuropath. Exp. Neurol.*, **14**, 198–213 (1955)
29. Gangloff, H., and Monnier, M., *Pflügers Arch. ges. Physiol.*, **261**, 421–33 (1955)
30. Cadilhac, J., *Hippocampe et épilepsie* (Paul Déhan, Ed., Montpellier, France, 205 pp. 1955)

31. French, J. D., Gernhardt, B. E., and Livingston, R. B., *Arch. Neurol. Psychiat.*, **75**, 260–74 (1956)
32. Segundo, J. P., Naquet, R., and Arana, R., *Arch. Neurol. Psychiat.*, **73**, 515–24 (1955)
33. Sawyer, C. H., and Gernandt, B. E., *Am. J. Physiol.*, **185**, 209–16 (1956)
34. Gozzano, M., Vizioli, R., and Ricci, G., *Riv. Neurol.*, **25**, 697–762 (1955)
35. Buser, P., and Rougeul, A., *J. Physiol. Path. gén.*, **47**, 121–23 (1955)
36. Cragg, B. G., and Hamlyn, L. H., *J. Physiol.*, **129**, 608–27 (1955)
37. Green, J. D., and Machne, X., *Am. J. Physiol.*, **181**, 219–24 (1955)
38. Machne, X., and Segundo, J. P., *J. Neurophysiol.*, **19**, 232–40 (1956)
39. Green, J. D., and Adey, W. R., *Electroencephalog. Clin. Neurophysiol.*, **8**, 245–62 (1956)
40. Gloor, P., *Electroencephalog. Clin. Neurophysiol.*, **7**, 223–42 (1955)
41. Gloor, P., *Electroencephalog. Clin. Neurophysiol.*, **7**, 243–64 (1955)
42. Koikegami, H., Fuse, S., Yokohama, T., Watanabe, T., and Watanabe, H., *Folia. Psychiat. Neurol. Japon.*, **8**, 336–70 (1955)
43. Koikegami, H., Yamada, T., and Usui, K., *Folia Psychiat. Neurol. Japon*, **8**, 7–31 (1954)
44. Mason, J. W., *Paper presented before the Endocrine Society* (Chicago, June, 1956)
45. Schreiner, L., and Kling, A., *Am. J. Physiol.*, **184**, 486–90 (1956)
46. Karll, P., *Compt. rend. soc. biol.*, **119**, 2227–29 (1955)
47. Terzian, H., and Dalle Ore, G., *Neurology*, **5**, 373–80 (1955)
48. Sawa, M., Yukiharu U., Masaya, A., and Toshio, H., *Folia Psychiat. Neurol. Japon.*, **7**, 309–29 (1954)
49. Heath, R. G., Monroe, R. R., and Mickle, W. A., *Am. J. Psychiat.*, **111**, 862–63 (1955)
50. Chapman, W. P., Schroeder, H. R., Geyer, G., Brazier, M. A. B., Fager, C., Poppin, J. L., Solomon, H. C., and Yakovlev, P. I., *Science*, **120**, 949 (1954)
51. Brady, J. V., and Nauta, W. J. H., *J. Comp. Physiol. Psychol.*, **48**, 412–20 (1955)
52. Harris, G. W., *Neural control of the pituitary gland.*, (Edward Arnold. Ltd., London; Williams & Wilkins, Baltimore, Md. 298 pp. 1955)
53. Harris, G. W., *Bull. Johns Hopkins Hosp.*, **97**, 358–75 (1955)
54. Benoit, J., and Assenmacher, I., *J. physiol. path. gén.*, **47**, 427–567 (1955)
55. Gloor, P., *Arch. Neurol. Psychiat.*, **71**, 773–90 (1954)
56. Gellhorn, E., *Neurology*, **6**, 335–343 (1956)
57. Gellhorn, E., and Redgate, E. S., *Arch. intern. pharmacodynamie*, **102**, 162–178 (1955)
58. Redgate, E. S., and Gellhorn, E., *Arch. intern. pharmacodynamie*, **102**, 179–186 (1955)
59. Gellhorn, E., Koella, W. P., and Ballin, H. M., *J. Psychol.*, **39**, 77–88 (1955)
60. Gellhorn, E., Koella, W. P., and Ballin, H. M., *Arch. intern. physiol.*, **62**, 381–89 (1956)
61. Gellhorn, E., Nakao, H., and Redgate, E. S., *J. Physiol.*, **131**, 402–23 (1956)
62. Redgate, E. S., and Gellhorn, E., *Arch. intern. pharmacodynamie*, **115**, 199–208 (1956)
63. Bein, H. J., *Ann. N. Y. Acad. Sci.*, **61**, 4–16 (1955)
64. Schneider, J. A., Holden, E., Rinehart, R., and Moore, R., *Am. J. Physiol.*, **181**, 64–68 (1955)
65. Schneider, J. A., Plummer, A. J., Earl, A. E., and Gaunt, R., *Ann. N. Y. Acad. Sci.*, **61**, 17–26 (1955)

66. Bhargava, K. P., and Borison, H. L., *J. Pharmacol.*, **115**, 464–79 (1955)
67. Rinaldi, F., and Himwich, H. E., *Diseases of Nervous System*, **16**, 133–41 (1955)
68. Harrison, F., and Goth, A., *J. Pharmacol.*, **116**, 262–67 (1956)
69. Feremutsch, K., *Monatschr. Psychiat. Neurol.*, **130**, 1–85 (1955)
70. Gregoretti, L., *Acta Neurovegetativa*, **12**, 25–40 (1955)
71. Andersson, B., and McCann, S. M., *Acta Physiol. Scand.*, **35**, 191–201 (1955)
72. Andersson, B., and McCann, S. M., *Acta Physiol. Scand.*, **35**, 312 (1956)
73. Maire, F. W., and Patton, H. D., *Am. J. Physiol.*, **184**, 345–50 (1956)
74. Maire, F. W., and Patton, H. D., *Am. J. Physiol.*, **184**, 351–55 (1956)
75. Grossman, R. G., and Wang, S. C., *Yale J. Biol. Med.*, **28**, 285–97 (1955/56)
76. Katsuki, S., Okajima, T., and Matsumoto, T., *Kumamoto Med. J.*, **8**, 180–86 (1955)
77. Grignon, G., *Compt. rend. soc. biol.*, **149**, 1457–959 (1955)
78. Mosier, H. D., *Endocrinology*, **57**, 661–69 (1955)
79. Sloper, J. C., *J. Anat.*, **89**, 301–16 (1955)
80. Adams, C. W. M., and Sloper, J. C., *J. Endocrinol.*, **13**, 221–28 (1956)
81. Abrahams, V. C., and Pickford, M,, *J. Physiol.*, **131**, 712–18 (1956)
82. Hagen, E., *Acta Anat.*, **25**, 1–33 (1955)
83. Anand, B. K., and Dua, S., *Indian J. Med. Res.*, **43**, 123–217 (1955)
84. Fedeli, S., Curri, S. B., and Tambuscio, S., *Arch. sci. med.*, **99**, 357–76 (1955)
85. Massopust, L. C., *Neurology*, **5**, 472–78 (1955)
86. Mayer, J., French, R. G., Zighera, C. F., and Barrnett, R. J., *Am. J. Physiol.*, **182**, 75–82 (1955)
87. Montemurro, D. G., and Stevenson, J. A. F., *Yale J. Biol. Med.*, **28**, 396–403 (1955/56)
88. Marshall, N. B., Barrnett, R. J., and Mayer, J., *Proc. Soc. Exptl. Biol. Med.*, **90**, 240–44 (1955)
89. Teitelbaum, P., *J. Comp. Physiol. Psychol.*, **48**, 156–63 (1955)
90. Fuller, J. L., and Jacoby, G. A., Jr., *Am. J. Physiol.*, **183**, 279–83 (1955)
91. Anand, B. K., Dua, S., and Shoenberg, K., *J. Physiol.*, **127**, 143–52 (1955)
92. Anand, B. K., and Dua, S., *Indian J. Med. Res.*, **43**, 113–22 (1955)
93. Greer, M. A., *Proc. Soc. Exptl. Biol. Med.*, **89**, 59–62 (1955)
94. Brobeck, J. R., Larsson, S., and Reyes, E., *J. Physiol.*, **132**, 358–64 (1956)
95. McCann, S. M., and Sydnor, K. L., *Proc. Soc. Exptl. Biol. Med.*, **87**, 369–73 (1954)
96. Fulford, B. D., and McCann, S. M., *Proc. Soc. Exptl. Biol. Med.*, **90**, 78–80 (1955)
97. Sobel, H., Levy, R. S., Marmorston, J., Schapiro, S., and Rosenfeld, S., *Proc. Soc. Exptl. Biol. Med.*, **89**, 10–13 (1955)
98. Martini, L., and De Poli, A., *J. Endocrinol.*, **13**, 229–34 (1956)
99. Martini, L., De Poli, A., and Curri, S., *Proc. Soc. Exptl. Biol. Med.*, **91**, 490–93 (1956)
100. Guillemin, R., and Hearn, W. R., *Proc. Soc. Exptl. Biol. Med.*, **89**, 365–67 (1955)
101. Swingle, W. W., Brannick, L. J., Barrett, W., LeBrie, S. J., and Parlow, A. F., *Proc. Soc. Exptl. Biol. Med.*, **91**, 223–26 (1956)
102. Briggs, F. N., and Munson, P. L., *Endocrinology*, **57**, 205–19 (1955)
103. Sawyer, C. H., Critchlow, B. V., and Barraclough, C. A., *Endocrinology*, **57**, 345–54 (1955)
104. Porter, J. C., and Jones, J. C., *Endocrinology*, **58**, 62–66 (1956)
105. Porter, J. C., and Rumsfeld, H. W., Jr., *Endocrinology*, **58**, 359–64 (1956)

106. Guillemin, R., and Rosenberg, B., *Endocrinology*, **57**, 599–607 (1955)
107. Saffran, M., and Schally, A. V., *Can. J. Biochem. Physiol.*, **33**, 408–415 (1955)
108. Anand, B. K., and Dua, S., *J. Physiol.*, **127**, 153–56 (1955)
109. Laqueur, G. L., McCann, S. M., Schreiner, L. H., Rosenberg, E., Rioch, D. M., and Anderson, E., *Endocrinology*, **57**, 44–54 (1955)
110. Greer, M. A., and Erwin, H. L., *Endocrinology*, **58**, 665–70 (1956)
111. Bogdanove, E. M., Spirtos, B. N., and Halmi, N. S., *Endocrinology*, **57**, 302–15 (1955)
112. Alloiteau, J., J., *Compt. rend.*, **242**, 931–33 (1956)
113. Tuchmann-Duplessis, H., and Mercier-Parot, L., *Compt. rend.*, **242**, 1233–1235 (1956)
114. Tuchmann-Duplessis, H., *Compt. rend.*, **242**, 1651–53 (1956)
115. Barraclough, C. A., and Sawyer, C. H., *Endocrinology*, **57**, 329–37 (1955)
116. Beach, F. A., Goldstein, A. C., and Jacoby, G. A., Jr., *J. Comp. Physiol. Psychol.*, **48**, 173–79 (1955)
117. von Euler, C., and Holmgren, B., *J. Physiol.*, **131**, 137–46 (1956)
118. Greer, M. A., *Endocrinology*, **57**, 755–56 (1955)
119. Ganong, W. F., Fredrickson, D. S., and Hume, D. M., *Endocrinology*, **57**, 355–62 (1955)
120. Roberts, S., and Keller, M. R., *Endocrinology*, **57**, 64–75 (1955)
121. Birzis, L., and Hemingway, A., *J. Neurophysiol.*, **19**, 37–43 (1956)
122. Anand, B. K., *Indian J. Med. Res.*, **43**, 195–99 (1955)
123. Sigg, E., Ochs, S., and Gerard, R. W., *Am. J. Physiol.*, **183**, 419–26 (1955)
124. Benetato, G., *J. physiol. path. gén.*, **47**, 391–403 (1955)
125. Auer, J., *J. Anat.*, **90**, 30–41 (1956)
126. Gardner, E., Thomas, L. M., and Morin, F., *Am. J. Physiol.*, **183**, 438–44 (1955)
127. Brandon, A., *Electroencephalog. Clin. Neurophysiol.*, **7**, 371–74 (1955)
128. Goldstein, L., and Minz, B., *J. physiol. path. gén.*, **47**, 591–603 (1955)
129. Minz, B., and Goldstein, L., *Compt rend. soc. biol.*, **149**, 1200–03 (1955)
130. Chauchard, P., Mazoué, H., and Lecoq, R., *J. physiol. path. gén.*, **47**, 130–32 (1955)
131. Cicardo, V. H., and Breiter, E., *Compt. rend. soc. biol.*, **149**, 1667–69 (1955)
132. Kojima, T., *Fukushima J. Med. Sci.*, **1**, 141–59 (1954)
133. Klopper, P. J., *J. Physiol.*, **129**, 547–53 (1955)
134. Kessler, M. M., *Yale J. Biol. Med.*, **28**, 351–62 (1955/56)
135. Beach, F. A., Zitrin, A., and Jaynes, J., *J. Exptl. Zool.*, **130**, 381–401 (1955)
136. Magoun, H. W., *High Blood Pressure Proceedings* (American Heart Association, Cleveland, Ohio, 186 pp., 1956)
137. Papez, J. W., *Electroencephalog. Clin. Neurophysiol.*, **8**, 117–28 (1956)
138. Papez, J. W., *Diseases of Nervous System*, **17**, 103–08 (1956)
139. Rossi, G. F., and Brodal, A., *J. Anat.*, **90**, 42–62 (1955)
140. Scheibel, M., Scheibel, A., Mollica, A., and Moruzzi, G., *J. Neurophysiol.*, **18**, 309–31 (1955)
141. Grastyán, E., Lissák, K., and Kékesi, F., *Acta Physiol. Acad. Sci. Hung.*, **9**, 133–51 (1956)
142. Lindgren, P., *Acta Physiol. Scand.*, **35**, Suppl. 121, 189 pp. (1955)
143. Tang, P. C., *J. Neurophysiol.*, **18**, 583–95 (1955)
144. Tang, P. C., and Ruch, T. C., *Am. J. Physiol.*, **181**, 249–57 (1955)
145. Anderson, E., Knowlton, K., Spence, W. T., McCann, S. M., Laqueur, G. L., Rioch, D. M.., and Haymaker, W., *Acta neurovegetativa*, **12**, 53–94 (1955)

146. Wise, B. L., *Proc. Soc. Exptl. Biol. Med.*, **91**, 557–60 (1956)
147. Katsuki, S., and Ikeda, Y., *Kumamoto Med. J.*, **4**, 135–41 (1952)
148. Katsuki, S., and Okajima, T., *Kumamoto Med. J.*, **6**, 20–27 (1953)
149. Katsuki, S., Okajima, T., Murakami, K., Shimada, H., Uramoto, T., and Teruya, T., *Kumamoto Med. J.*, **8**, 133–44 (1955)
150. Katsuki, S., and Ogata, H., *Kumamoto Med. J.*, **5**, 86–95 (1953)
151. Russell, G. V., *Texas Repts. Biol. Med.*, **13**, 939–88 (1955)
152. Baxter, D. W., and Olszewski, J., *J. Neurophysiol.*, **18**, 276–87 (1955)
153. Walberg, F., *J. Comp. Neurol.*, **104**, 77–173 (1956)
154. Mitchell, G. A. G., and Warwick, R., *Acta Anat.*, **25**, 371–95 (1955)
155. Yoshii, N., Horiuchi, K., Higashida, S., and Okamoto, C. *Folia Psychiat. Neurol. Japon.*, **8**, 303–11 (1955)
156. Metz, B., *Am. J. Physiol.*, **185**, 142–44 (1956)
157. Duchême-Marullax, P., and Arnould, P., *J. physiol. path. gén.*, **47**, 363–72 (1955)
158. Bell, F. R., and Lawn, A. M., *J. Physiol.*, **128**, 577–92 (1955)
159. Malméjac, J., Chardon, G., and Neverre, G., *Compt. rend. soc. biol.*, **119**, 2171–74 (1955)
160. Clemente, C. D., and Van Breemen, V. L., *Anat. Record*, **123**, 65–79, (1955)
161. Amols, W., and Merritt, H. H., *Neurology*, **5**, 645–53 (1955)
162. Tauc, L., *J. physiol. path. gén.*, **47**, 769–92 (1955)
163. Tauc, L., *Compt. rend.*, **241**, 1070–73 (1955)
164. Tauc, L., *Compt. rend.*, **242**, 676–78 (1956)
165. Eccles, R. M., *J. Physiol.*, **130**, 572–84 (1955)
166. Oscarsson, O., *Acta Physiol. Scand.*, **35**, 152–66 (1955)
167. Downmann, C. B. B., *J. Neurophysiol.*, **18**, 217–35 (1955)
168. Edwards, C., and Larrabee, M. G., *J. Physiol.*, **130**, 456–66 (1955)
169. Covian, M. R., and Cordero Funes, J. R., *J. Neurophysiol.*, **18**, 353–61 (1955)
170. Robertson, J. D., Swan, A. A. B., and Whitteridge, D., *J. Physiol.*, **131**, 463–72 (1956)
171. Dempsher, J., Larrabee, M. G., Bang, F. B., and Bodian, D., *Am. J. Physiol.*, **182**, 203–16 (1955)
172. Florey, E., and McLennan, H., *J. Physiol.*, **129**, 384–92 (1955)
173. Lissák, K., and Endrőczi, E., *Acta Physiol. Acad. Sci. Hung.*, **9**, 111–21 (1956)
174. Varagić, V., *J. Physiol.*, **132**, 92–99 (1956)
175. McEwen, L. M., *J. Physiol.*, **131**, 678–89 (1956)
176. Pascoe, J. E., *J. Physiol.*, **132**, 242–55 (1956)
177. Emmelin, N., and MacIntosh, F. C., *J. Physiol.*, **131**, 477–96 (1956)
178. Kostial, K., and Vouk, V. B., *J. Physiol.*, **132**, 239–41 (1956)
179. Hutter, O. F., and Kostial, K., *J. Physiol.*, **129**, 159–66 (1955)
180. Hazard, R., Corteggiani, E., and Renier-Cornec, A., *Compt. rend. soc. biol.*, **149**, 1874–78 (1955)
181. Loewenstein, W. R., *J. Physiol.*, **132**, 40–60 (1956)
182. Hutter, O. F., and Loewenstein, W. R., *J. Physiol.*, **130**, 559–71 (1955)
183. Malméjac, J., *J. Physiol.*, **130**, 497–512 (1955)
184. Matthews, R. J., Jr., *J. Pharmacol.*, **116**, 433–43 (1956)
185. Schmitt, H., and Gonnard, P., *Compt. rend. acad. sci.*, **240**, 2573–75 (1955)
186. Beck, H., and Veil, C., *Compt. rend.*, **242**, 279–82 (1956)
187. Strömblad, R., *Acta Physiol. Scand.*, **34**, 38–58 (1955)
188. Strömblad, B. C. R., *Acta Physiol. Scand.*, **36**, 47–65 (1956)
189. Strömblad, B. C. R., *Acta Physiol. Scand.*, **36**, 137–53 (1956)

190. Strömblad, B. C. R., *Acta Physiol. Scand.*, **36**, 154–57 (1956)
191. Strömblad, B. C. R., *Acta Physiol. Scand.*, **36**, 158–70 (1956)
192. Emmelin, M. G., and Strömblad, B. C. R., *Acta Physiol. Scand.*, **36**, 171–74 (1956)
193. Perry, W. L. M., and Reinert, H., *J. Physiol.*, **130**, 156–66 (1955)
194. Donovan, B. T., and van der Werff ten Bosch, J. J., *J. Physiol.*, **132**, 123–129 (1956)
195. Descomps, H., Saint-Saens, M., Theiler, R. M., and Miravet, L., *Compt. rend. soc. biol.*, **119**, 2143–48 (1955)
196. Descomps, H., and Theiler, R., *Compt. rend. soc. biol.*, **119**, 2141–43 (1955)
197. Kelentei, B., *Acta Physiol. Acad. Sci. Hung.*, **8**, 165–72 (1955)
198. de Takats, G., *Surgery*, **38**, 915–27 (1955)
199. Cervoni, P., West, T. C., and Fink, L. D., *J. Pharmacol.*, **116**, 90–97 (1956)
200. Fleming, D. G., and Olmstead, J. M. D., *Am. J. Physiol.*, **181**, 664–68 (1955)
201. Emmelin, N., *Acta Physiol. Scand.*, **34**, 11–21 (1955)
202. Emmelin, N., *Acta Physiol. Scand.*, **34**, 29–37 (1955)
203. Eayrs, J. T., and Baddeley, R. M., *J. Anat.*, **90**, 161–71 (1956)
204. Wyss, O. A. M., *Yale, J. Biol. Med.*, **28**, 471–80 (1955/56)
205. Meulders, M., *Compt. rend. soc. biol.*, **149**, 1301–04 (1955)
206. Witzleb, E., Bartels, H., Budde, H., and Mochizucki, M., *Pflügers Arch. ges. Physiol.*, **261**, 211–18 (1955)
207. McGubbin, J. W., Green, J. H., Salmoiraghi, G. C., and Page, I. H., *J. Pharmacol.*, **116**, 191–97 (1956)
208. Terzioglu, M., Göral, C., and Bardavit, J., *Am. J. Physiol.*, **182**, 100–04 (1955)
209. Hodgson, E. S., Lettvin, J. Y., and Roeder, K. D., *Science*, **122**, 417–18 (1955)
210. Blood, F. R., Kosman, M. E., and D'Amour, F. E., *Am. J. Physiol.*, **182**, 180–82 (1955)
211. Severinghaus, J. W., and Stupfel, M., *J. Appl. Physiol.*, **8**, 81–87 (1955)
212. Douglas, W. W., and Schaumann, W., *J. Physiol.*, **132**, 173–86 (1956)
213. Douglas, W. W., Ritchie, J. M., and Schaumann, W., *J. Physiol.*, **132**, 187–98 (1956)
214. Kuntz, A., and Napolitano, L. M., *J. Comp. Neurol.*, **104**, 17–31 (1956)
215. Montgomery, A. V., and Holmes, J. H., *Am. J. Physiol.*, **182**, 227–31 (1955)
216. Dussardier, M., *J. physiol. path. gén.*, **47**, 170–73 (1955)
217. Iggo, A., *J. Physiol.*, **128**, 593–607 (1955)
218. Iggo, A., *J. Physiol.*, **131**, 248–56 (1956)
219. Towbin, E. J., *Am. J. Physiol.*, **182**, 377–82 (1955)
220. Code, C. F., and Watkinson, G., *J. Physiol.*, **130**, 233–52 (1955)
221. Imparato, A. M., Reid, L. C., and Hinton, J. W., *Am. J. Physiol.*, **184**, 418–27 (1956)
222. Guth, L., *Am. J. Physiol.*, **185**, 205–08 (1956)
223. Hunt, J. N., *J. Physiol.*, **132**, 267–288 (1956)
224. Milton, G. W., and Smith, W. M., *J. Physiol.*, **132**, 100–14 (1956)
225. Gray, G. W., Hendershot, L. C., Whitrock, R. M., and Seevers, M. H., *Am. J. Physiol.*, **181**, 679–87 (1955)
226. Garry, R. C., and Gillespie, J. S., *J. Physiol.*, **128**, 557–76 (1955)
227. Lévy, J., and Michel-Ber, E., *J. physiol. path. gén.*, **47**, 575–90 (1955)
228. Ogle, W. S., French, L. A., and Peyton, W. T., *J. Neurosurg.*, **13**, 81–87 (1956)
229. Comarr, A. E., and Kaufman, A. A., *J. Neurosurg.*, **13**, 95–106 (1956)

HEARING[1]

By I. Tasaki

Laboratory of Neurophysiology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Dept. of Health, Education and Welfare, Bethesda, Maryland

In this review an attempt is made to survey the recent developments in the physiology of hearing which took place since the last review on this subject by Ades (1) was published four years ago. We are concerned in this review mainly with the progress in our understanding of the function of the cochlea where auditory stimuli are converted into transportable informations in the nervous system, i.e., into nerve impulses. We shall not go into the biophysics of the tympanic membrane and the middle ear; this topic has been thoroughly and authoritatively reviewed by von Békésy & Rosenblith in the Handbook of Psychology (14) and by Wever & Lawrence in their recent monograph (132). Neurophysiological problems at various levels along the auditory pathway from the medulla to the cortex will be discussed only to a limited extent; there is an extensive review on this subject by Galambos (45). Psychophysical and pathological phenomena are outside the scope of the present review.

The recent progress in our understanding of the process hearing is brought about (*a*) by the discovery of the huge steady (D.C.) potential in the cochlea by Békésy (7, 8) and by the investigation into the source of this potential by Davis and his associates (27, 112), (*b*) by the recent studies on the origin and the significance of the cochlear microphonic responses by the use of the modern microelectrode technique (8, 112, 113), and (*c*) by direct recording of nerve impulses in individual fibers in the auditory nerve (110, 111), and by other experimental findings. The present review is prepared with a view to showing to students of auditory physiology and to investigators in other fields of physiology how these recent experiments were carried out, what these findings imply, and, if possible, what are the next problems to be investigated in this field of physiology.

Electroanatomy of The Cochlea

The term "electroanatomy" was introduced by Békésy in his paper describing the electric potential and the resistivity in various parts of the cochlea in relation to its structure (5). Most of the experiments along this line were done on the exposed cochlea of the anaesthetized guinea pig. There is good evidence, however, that the main conclusions drawn from the observations on the guinea pig apply also to the cat cochlea.

It is simple to open the air-filled bulla of the guinea pig or the cat and, after appropriate fixation of the head of the animal, to introduce a micro-

[1] The survey of literature pertaining to this review was completed in May 31, 1956.

pipette into the cochlea through the transparent membrane covering the round window. With adequate illumination one can see, through the round window, a part of the basilar membrane near its basal end. The space between the round window and the basilar membrane is occupied by the perilymph filling this part of the scala tympani. On penetrating the round window with a glass-pipette electrode one finds that the electric potential of this perilymph is very close to the potential of the wet cotton placed on a neighboring uninjured muscle. For simplicity's sake in the following description, let us take this perilymph near the round window as the reference point in mapping out the distribution of potentials in the cochlea.

As the microelectrode is pushed further toward the basilar membrane, the potential at the tip of the microelectrode is found to stay constant until the electrode reaches the basilar membrane. The conductivity of the perilymph is as high as that of other body fluids (5, 105), and the space occupied by this fluid in the scala tympani (basal turn) is practically equipotential. As soon as the microelectrode starts piercing the structure on the basilar membrane, irregular, negative potentials are observed (cf. 8, 112). The negativity is often as high as 50 to 80 mv if the tip diameter of the electrode is smaller than about 1μ. This appears to be the resting potential of the cellular elements in this region; the present reviewer has some evidence indicating that this negative potential is greatly reduced when the major portion of the perilymph in the scala tympani is replaced with isotonic potassium chloride solution.

When the microelectrode is pushed further through the basilar membrane, one finds that the potential at the tip of the electrode suddenly jumps to the level 70 to 85 mv above zero. This large positive potential, which may be called the *steady* (or D.C.) *cochlear potential* can be observed very easily with a glass-pipette electrode of as large as 20μ in diameter filled with either the ordinary Ringer solution or isotonic KCl solution. When a microelectrode with a tip diameter smaller than 1μ is used, it is possible to repeat this observation many times without any appreciable loss in the size of the steady potential.

The conclusion that the steady cochlear potential is associated with the space occupied by the endolymph was drawn from Békésy's observation (8) in which he explored the steady potential from the other side of the scala media, namely through Reissner's membrane. In the apical turn of the guinea pig cochlea it is possible to remove the bony wall covering the scala vestibuli and observe the cellular elements in the scala media directly through Reissner's membrane.

It was shown by these experiments that there is no large potential difference between the fluids in the scala vestibuli and the scala tympani. The potential inside the noncellular tectorial membrane is the same as that of the endolymph. The tissue fluid in the spiral ligament outside the stria vascularis is equipotential to the perilymph. Penetration of a microelectrode across the stria vacularis into the scala media results in a sudden rise in po-

tential by the same amount (112). Various cellular elements in the wall of the endolymphatic space are found to show negative potentials when penetrated with a hyperfine microelectrode (8, 112).

The discovery of the huge steady potential between the peri- and endolymph immediately raised the question as to how it is generated and maintained. The recent chemical determination of the concentrations of monovalent ions in the cochlea by Smith, Lowry & Wu (105) indicates that the vestibular endolymph contains surprisingly high potassium (144 m.eq.), low sodium (15.8 m.eq.) and high chlorine (107 m.eq.) concentrations, while the perilymph has almost the same ionic composition as the spinal fluid (approximately 150 m.eq. of Na, 4.5 m.eq. of K, and 122 m.eq. of Cl). Their analysis of the cochlear endolymph was not as satisfactory as that of the vestibular endolymph but it suggested that the ionic composition of the endolymph was the same in the cochlea and in the utricle.

In spite of the fact that the ionic composition of the endolymph is unique among various body fluids, the concentration gradient for potassium or sodium ions between the peri- and endolymph does not seem to be directly related to the potential difference between the two fluids. The reasons are:

1. Practically complete replacement of the perilymph in the scalae vestibuli and tympani with an isotonic KCl solution or a sodium-free (choline) or chlorine-free (glutamate) Ringer solution does not immediately alter the steady potential (27).

2. All the attempts to demonstrate the existence of the large potential in the vestibular endolymph (unpublished observations) were unsuccessful, and the present reviewer believes that the positivity of the utricular endolymph (which was used in the above mentioned chemical analysis by Smith *et al.*) is about 5 mv or less.

3. If one assumes that the membrane of the cells surrounding the endolymphatic space are selectively permeable to potassium ions, the sign of the observed endolymphatic potential is opposite to what is expected.

There is strong evidence indicating that this steady potential of the cochlea is maintained by oxidative metabolism (7, 27). A reduction in the blood oxygen tension, caused by inhalation of pure nitrogen or by obstruction of the tracheal cannula, reduces the endolymphatic potential significantly within one or two minutes. If oxygen is readmitted before the heart beat stops, there is always a prompt recovery of the potential within 2 or 3 sec. This enormous rapidity in recovery of the potential is an indication of the dependence of the potential on the oxidative metabolism as opposed to the ionic concentration gradient between the peri- and endolymph. Injection of azide or cyanide into the scala media depressed the steady potential, but injection of a small amount (approximately 0.2 c.mm.) of an isotonic KCl or NaCl solution had little or no immediate effect on this potential (27). The size of this potential is insensitive to the depth of anaesthesia. It seems desirable in this connection to determine whether or not there is a large gradient in the hydrogen ion concentration across the wall of the endolym-

phatic space; at present there is no reliable measurement of pH of the endolymph. [For further information about the chemical compositions of the endolymph, cf. Smith *et. al.*, (105) and Jensen & Vilstrup (66, 67)].

The existence of a large potential difference across the wall of the endolymphatic space suggests that this wall may show a high resistance to a direct current. In fact it was found that this is actually the case. As a consequence, this wall forms a small (approximately 0.1 mm.^{2} in cross section) but long (approximately 20 mm. in length) tube of a resistive membrane, enclosing the highly conductive endolymph and suspended in the conductive perilymph [cf. recent anatomical data by Fernández (36), Wever & Lawrence (132), and Hilding (58)]. It is expected, therefore, that the endolymphatic space shows the property of a "core-conductor," along which a potential difference applied at one point of the system tends to spread. This spread of potential, however, is not as extensive as postulated by Békésy [Fig. 3 in (11)].

In connection with the discovery of the huge endolymphatic potential, Békésy describes a small (approximately 3 mv) potential difference between the perilymph in the apex and the perilymph near the round window. The present reviewer confirmed this observation on several occasions. If one assumes that this potential is genuine and unrelated to the holes drilled in the cochlea, the logical consequence will be that the endolymphatic potential at the apex is less than that near the round window (by about 10 mv). A potential difference in the highly conducting fluid indicates the existence of a strong steady current along the cochlea. The significance of this small potential is still obscure.

A hypothesis has been put forward attributing the source of the cochlear steady potential to the function of the stria vascularis [Davis, (22)]. The exploration of the potential field in the cochlea (112) does not seem to support this hypothesis. Engström & Wersäll (34) describe the presence of a rich system of minute filiform processes on the outer surface of the Hensen cells and discuss its possible role in the function of the hair cells.

Origin of Cochlear Microphonics

A simple, clear-cut experiment which serves to localize the origin of the chochlear microphonics is to observe small electrical responses to a weak continuous tone during penetration of a recording microelectrode through the structure on the basilar membrane. [This observation is an extension by Tasaki *et al.* (112) of the gross localization of the origin of the microphonics by Davis *et al.* (26) and by Békésy (8).] Both in cats and guinea pigs, this can be done by pushing either a Ringer filled 3μ micropipette or an ordinary submicroscopic microelectrode first through the round window membrane, then through the basilar membrane under direct visual control. If one uses a low gain D.C. amplifier for recording the steady potential simultaneously with a high-gain A.C. amplifier (connected to the same microelectrode), one can easily correlate the appearance of the steady endolymphatic potential

with the change in the microphonic response. By triggering the sweep of the high-gain channel of the oscillograph by the oscillator giving rise to a low frequency tone (e.g., 500 c.p.s.), it is possible to determine changes in the phase of the microphonic response during penetration. The indifferent electrode could be placed on the neck of the animal.

When the tip of the microelectrode is making contact with the perilymph between the round window and the basilar membrane, there is a sinusoidal microphonic response which varies proportionately as the intensity of the applied pure tone. When the recording electrode reaches the region of the spiral organ of Corti above the basilar membrane, the amplitude of this microphonic response increases two or three fold without any appreciable change in its phase. Then, at the moment when the huge endolymphatic potential appears on further advancement of the electrode, the phase of the microphonic response suddenly reverses, its amplitude being still very large. While the electrode travels through the endolymphatic space, the phase and the amplitude of the microphonics stay practically constant. When the electrode is advanced further and penetrates through Reissner's membrane, there is a sudden reduction in the amplitude of the microphonics without any appreciable change in their phase (see Fig. 1).

The significance of this observation is clear: it indicates that the microphonic response is generated at or near the interface between the endolymph and the space occupied by the spiral organ of Corti. (Note that in any network consisting of a battery and many resistors the largest change in potential is observed when the probe-electrode is moved from one terminal of the battery to the other.) This interface is obviously the stiff layer of reticular lamina through which the hair-bearing ends of the hair cells are known to perforate. Phase-microscopic studies of the organ of Corti and the tectorial membrane have recently been made (57, 70).

There are several additional pieces of direct evidence in support of the old hypothesis that hair cells are the generators of the microphonics. It has been shown (112, 114) that an isotonic KCl solution introduced in the scala tympani of the basal turn eliminates both the microphonics and the action potentials of the auditory nerve elicited by sound stimuli (either clicks or tone pips) within about 5 sec. after application. This observation indicates that the basilar membrane is permeable to KCl and consequently the nerve fibers and the hair-cells are exposed to this electrolyte introduced into scala tympani. If the KCl solution is introduced into the scala vestibuli, there is no clear effect upon these responses to sounds. The highly resistive membrane surrounding the endolymphatic space is evidently impermeable to potassium ions. The significant corollary of this observation is that the diffusion barrier between the endolymph in scala media and the perilymph in scala tympani is not the basilar membrane, but it is the reticular lamina. The spiral organ of Corti is immersed, not in the endolymph which seems to have a high potassium content, but in the perilymph which contains sodium as the predominant cation.

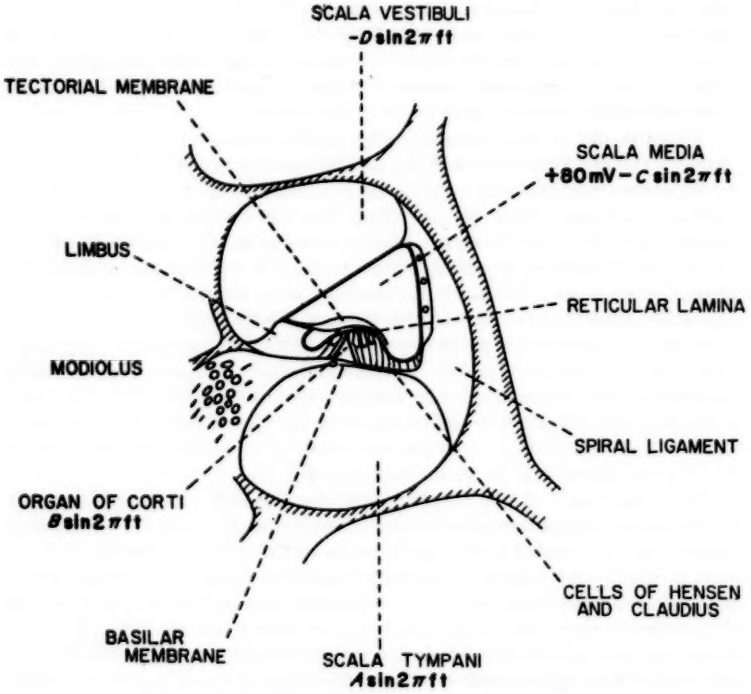

FIG. 1. Diagrammatic cross section of a cochlear canal. Heavy letters indicate the distribution of the steady and the microphonic potentials. Symbol f represents the frequency of the applied sound, t, time, A, B, C and D, the amplitude of the microphonics. In the guinea pig cochlea stimulated with a low tone, the ratio A:B:C:D is approximately 1:3:3:1.

Beside the spiral organ the cells of Hensen and Claudius lie on the basilar membrane; but these cells are not responsible for the generation of the microphonic response, since a microelectrode inserted in the layer of these cells picks up very little or no microphonic activity (8, 112). The microphonic response can be markedly reduced by injection of small amounts of poisons, such as azide, cyanide, or cocaine into the scala media. In the case of cocaine, the microphonic response is eliminated without any loss in the steady potential of the endolymph. A direct current which tends to increase the potential difference across the reticular lamina augments the microphonic response: a current flowing in the opposite direction suppresses it (112, 114).

All these findings attest to the conclusion that the microphonic response is generated at the hair-bearing end of the hair cells. Across this hair-bearing

end there is at rest a potential difference of about 150 mv, i.e., the sum of the steady endolymphatic potential and the resting potential of the hair cells. The mechanical displacement of the spinal organ seems to cause a variation in this huge resting potential. This variation in potential causes a flow of current in the surrounding conducting medium in the following pathway: hair cell, endolymph, Reissner's membrane, perilymph in the scala vestibuli, perilymph in the spiral ligament, perilymph in the scala tympani, hair cell. This pattern of current flow explains the distribution of the microphonic response in and around the cochlea.

There is an error in the interpretation of the data in an earlier paper by Davis, Tasaki & Goldstein [Fig. 3 in (26)]. The observed points in the drawing are reliable but the position of the equipotential lines connecting these points are incorrect. Large sudden changes in the microphonic potential are localized at the wall of the endolymphatic space.

Békésy seems to assume that the basilar membrane, instead of the reticular lamina, is the main diffusion barrier between the scala media and tympani [Fig. 3 in (11)]. It appears impossible to the present reviewer to interpret, under this assumption, the phase reversal of the microphonics at the reticular lamina and the quick action of the potassium solution introduced into the scala tympani.

The relationship between the mechanical movement of the spiral organ and the phase of the microphonic response was investigated by Békésy with his vibrating electrode (6, 10). He removed Reissner's membrane and moved various elements on the basilar membrane with his recording electrode. This procedure is certainly subject to the criticism that the state of the hair cells examined might have been entirely abnormal. (Note that a marked reduction in the steady cochlear potential by injection of drugs or by surgical injury is always associated with a significant loss of microphonic responses.) A potential variation of a few millivolts can easily be generated by a slight movement of the electrode making contact with a cell.

In spite of these limitations in his technique, Békésy's conclusion that the microphonic response is directly proportional to the displacement, and not to the velocity, of the elements on the basilar membrane appears to be correct. A steady flow of perilymph causing a steady displacement of the scala media generates a steady decrease or increase in the D.C. potential in scala media, depending on the direction of the displacement caused by the flow [Tasaki *et al.* (112)]. A high hydrostatic pressure in the scala vestibuli, causing a displacement of the basilar membrane toward scala tympani, increases the endolymphatic potential, and vice versa.

The effect of oxygen deprivation upon the cochlear microphonics has been investigated recently by Bornschein & Krejci (17), by Tonndorf *et al.* (121), and by Fernández (37).

Pattern of Motion of the Cochlear Partition set up by Sound

The phrase "cochlear partition" has been introduced by Békésy (4) to indicate the assembly of Reissner's membrane, tectorial membrane spiral organ, cells of Hensen and Claudius, and basilar membrane. This whole

structure is known to move more-or-less in unison in response to sound stimulation [Békésy (9)]. Now, it is possible to investigate the motion of the cochlear partition taking the microphonic responses generated by sound as an index. Since the microphonic response at a given point in the cochlea appears to be proportional to, and in phase with, the displacement of the cochlear partition, and since electrical signals can be amplified and measured with great ease, the electrical method of mapping out the pattern of motion of the cochlear partition is expected to yield interesting results which can be correlated with the results of Békésy's optical measurements on post mortem specimens (4).

A problem to be solved before the electrical signs of the motion of the cochlear partition can be used for the study of the motion itself is the estimation of the extent of current spread in the cochlea. This problem has been solved, at least to the present reviewer's satisfaction. By the use of a pair of differential electrodes placed across the cochlear partition (one in the scala vestibuli and the other in the scala tympani), "it is possible to record cochlear microphonic from a short segment (about 1 mm.) of the cochlear partition" (113). There is, however, an entirely contradictory viewpoint expressed by Wever & Lawrence (131, 132).

The statment just quoted is based primarily on the experimental fact that the cochlear microphonics having a phase difference of 90 degrees can be recorded by the differential method at two points in the third turn separated by about 1 mm. [p. 505 in (113)]. If one assumes, as Wever & Lawrence did [Fig. 111 in (132)], that the microphonic response generated at one point in the cochlear partition spread very extensively in the cochlea, it would be impossible to explain this experimental fact.

The cochlear microphonics are generated, as has been stated in the preceding section, primarily across the reticular lamina. The potential tends to spread along the tubing consisting of the wall of endolymphatic space. Since, however, there is a capacitative flow of current through this wall, the attenuation of the microphonic response along the cochlear partition should be much greater than that of a direct current. There is another factor which tends to reduce the spread of the microphonic response in the cochlea: that is the electric connection of the scalae, vestibuli and tympani, by the perilymph in the spiral ligament (see Fig. 1). Because of this shunting effect, the potential difference between these two scalae is expected to attenuate, with increasing distance from the active locus, more rapidly than the potential difference between scala media and tympani (or vestibuli) does.

A sinusoidal voltage applied near the round window of the guinea pig cochlea through a pair of glass microelectrodes (one in scala media and the other in scala tympani) is found to attenuate in the basal turn at a rate of 4 to 6 db per mm. in the frequency range between 200 and 6000 cp.s. (unpublished data by the reviewer). The attenuation is considered to be more marked in the upper turns than in the basal turn, because of the greater shunting effect of the spiral ligament. Wever & Lawrence [Fig. 110 in (132)]

measured the spread of electricity in the cochlea and gave a rate of attenuation as low as 1 db per mm. The source of the error in their measurement is obvious; they made an assumption that the spread of electricity can be measured by using a unipolar electrode (a single electrode placed on the cochlea referred to the indifferent electrode on the neck). It should be noted that the potential difference between the apex and the neck is not equal to zero even when the potential gradient (or the current) is limited in the basal turn [cf. Fig. 4 (113)].

It has been known for many years [see Wever (129)] that the amplitude of the microphonic response recorded with an electrode on the round window (the other on the neck of the animal) depends only slightly on the frequency of the sound. The microphonics in the basal turn recorded by the differential method show almost exactly the same frequency-dependence as the response at the round window [Figs. 5 and 6 in (113)]. The microphonics recorded differentially in the third turn, on the contrary, show a marked reduction in amplitude when the frequency of sound is raised above 1 kc.; for frequencies higher than 2.5 kc., there is practically no observable response in the third turn. In other words, the response of the upper turn is limited to low frequency tones, while the basal end of basal turn responds to any audible frequency.

For the reasons mentioned above, it is not possible to attribute the microphonic response of the basal turn to low frequency sound to a spread of electricity from the apical part of the cochlea. It has been shown in this connection that the response from the third turn can be almost completely eliminated without affecting the basal turn responses simply by injecting a small amount of isotonic KCl solution into the apex (114). It is also possible to eliminate the basal turn microphonics with KCl without affecting the third turn responses. A polarizing current applied in the basal turn modifies the microphonics from the basal turn but not the responses from the third turn (114). All these experiments prove that, by this differential method, the responses from different turns are recorded separately. The observation mentioned in the preceding section, namely, an increase in amplitude followed by a reversal in phase of a low frequency microphonic response on penetration of the recording microelectrode through the structure on the basilar membrane, can by no means be interpreted in terms of a spread of electricity from a distant active area. An interesting corollary of this statement is that the response recorded at the round window does not reflect the activity of the whole cochlea, but it only reflects the activity near the basal end of the basal turn. This has never been clearly understood in the past [e.g., Keidel & Sick (75)].

The statement just made may raise a question: why is the microphonic response to a low tone so large in the basal turn where there is very little mechanical movement? The answer to this question is not very obvious. It is possible that a small displacement in the basal turn causes a relatively large stress in the hair-cells, thus generating relatively large microphonics.

The microphonic response to a 500 c.p.s. tone is larger in the third turn than in the basal turn, the difference being about 10 db or slightly more depending on the position of the two differential electrodes. The vibratory motion in the middle of the basal turn estimated by Békésy by extrapolation [Fig. 32 in (14)] seems to have an amplitude of the order of one tenth of the value at the point of maximum vibration in the upper turn, This disagreement, therefore, between the present electrical data and the previous optical data on this point does not seem to be very serious.

Another point of apparent inconsistency between the electrical and optical data has been discussed by Zwislocki (142). When the frequency of a tone is varied continuously, the amplitude of mechanical vibration at a point in the cochlea first increases slowly with increasing frequency and, after a maximum is reached, the amplitude drops very rapidly. The results obtained by the electrical method agree with the optical data in demonstrating the rapid fall in amplitude for frequencies higher than a value characteristic of the point in the cochlea; however, the electrical data did not show any fall in amplitude with decreasing frequency. Zwislocki explained this discrepancy to be due to the difference in the experimental conditions employed in two cases: in Békésy's experiment the amplitude of the stapes movement was held constant at different frequencies, while in that of Tasaki *et al.* the amplitude of the electrical response near the round window was kept constant.

Except in these somewhat minor points, the electrical data are in excellent agreement with the optical data. The pattern of traveling waves in the cochlea demonstrated by the electrical method supports, beyond any reasonable doubt, the legitimacy of Békésy's arguments based on his earlier observation on cochlear specimens taken from fresh human cadavers (4). By recording microphonics simultaneously at two different turns of the cochlea and using tone pips as sound stimuli (113), the time required for the vibratory wave to travel along the cochlear partition has been measured. Recording Lissajous figures formed by the microphonic responses led off from two different turns, phase differences between the vibrations at different turns in the cochlea have been determined.

One of the advantages of the electrical method of investigating the motion of the cochlea over the optical method is that there is no limitation as to the type of sound stimuli that can be employed. In the optical method, observations have to be limited to low frequency pure tones. The disadvantage of the electrical method lies naturally in the more-or-less indirect relationship between the mechanical motion of the cochlear partition and its electrical signs; but this disadvantage is well compensated by the situation that the generation of microphonics appears to be an essential intermediate step intervening between the mechanical motion and initiation of nerve impulses in the cochlea [cf. e.g., Wever (129), Davis *et al.* (26), Tasaki (110), and Tonndorf *et al.* (121)].

Physicomathematical investigations into the nature of the traveling

waves were recently reported by Zwislocki (139), Peterson & Bogert (89), and by Fletcher (38). An observation on a mechanical model of the chochlea was made by Diestel (30). The historical development of the concept of traveling waves can be found in a recent monograph and in an article by Wever & Lawrence (132, 131).

In connection with the traveling waves in the cochlea, there is an apparently paradoxical phenomenon investigated independently by two different groups of investigators [Tasaki *et al.* (113); Wever & Lawrence (130)]. A sound stimulus applied to the cochlea through a small hole drilled through its b ɔny wall near the apex generates a wave which travels in the usual direction, namely from the basal turn towards the apex. Békésy saw this phenomenon some time ago in his model before he renewed his study on it (12). This phenomenon is evidently due to initiation of a slowly traveling transverse wave in the basal turn by the longitudinal (compressional) wave starting near the apex and traveling toward the round window (79, 113, 140). Wever & Lawrence (130, 131), being reluctant to accept the existence of traveling waves in the cochlea, explained the same phenomenon differently [cf. also (134)]. The fact that the vibration pattern in the cochlear partition is independent of the path by which the sound is applied is very important in considering the process of hearing by bone conduction [Zwislocki (140)].

Nerve Impulses in Auditory Nerve Fibers

It is well known that the potential recorded with an electrode placed on or near the cochlea (with the other indifferent electrode on the neck of the animal) is a mixture of the microphonic response and the response of the auditory nerve. Davis and his associates (25, 113) developed an electronic method of separating the two kinds of responses of the cochlea to sound stimuli. The principle of the method is based on the fact that the microphonic response in the scala vestibuli (basal turn) is opposite in phase to that of the scala tympani, while the neural responses have the same size and phase in the two scalae. The method of recording neural responses used by Rosenblith & Rosenzweig (96, 98) is based on the same principle; by placing a recording electrode on a suitable location on the bony surface of the cochlea, it is possible to obtain records of neural responses uncontaminated by microphonic responses.

Neural responses to short pip or to click stimuli were recorded from various locations in the cochlea with a view to finding the sources of the nerve action potentials [Davis *et al.* (26)]. The main spike potential (so called N_1), which is negative in the cochlea, is found to represent the acitvity of the nerve fibers between the modiolus and the internal auditory meatus. The action potential arising in the portion of the nerve in the bony canal between the basilar membrane and the modiolus can be observed in a differential recording between the scala vestibuli and tympani; since this early portion of the nerve action potential displaces the base-line of the recorded microphonics, it was once considered as the sign of an excitatory process (i.e., the

summating potential) intervening between the microphonic and neural responses [Davis, Fernández & McAuliffe (25)]. Goldstein (50) investigated a different type of displacement of the base-line in recording microphonic responses; it occurs during asphyxia or after surgical injury of the cochlea and is unrelated to nerual activities [cf. also Fernández (37)].

The auditory nerve fibers in the modiolus are 2.5 to 4μ in diameter (42). It was found possible to record action potentials from individual fibers in the auditory nerve [Tasaki (110), Tasaki & Davis (111)] by the use of submicroscopic microelectrodes developed by Ling & Gerard (81). The latency, size and shape of the responses, as well as the position of the microelectrodes, assured that the records were taken from the axons of the primary neurones in the auditory pathway. These microelectrode studies have clarified the following problems which arose from the observation of responses of cell-bodies in the cochlear nucleus by Galambos & Davis (46) and by Galambos (43):

Absence of inhibition by sound.—Most of the auditory nerve fibers show spontaneous discharges of impulses in absence of acoustical stimuli to the ear. These spontaneous discharges cannot be suppressed by application of sounds. A discharge of impulses induced by a tone cannot be suppressed by superposing a second tone upon the first. The phenomenon of inhibition observed by Galambos (43) under similar conditions is the property of the cell-body in the cochlear nucleus (probably dorsal) in the medulla and not that of the afferent nerve fibers in the auditory system.

Response area.—In a chart relating intensities and frequencies of various tones, the area occupied by points representing effective (suprathreshold) tones for a given neural element is generally termed a "response-area" for the element. For a single auditory nerve fiber, the response area is bound by a line indicating a sharp rise in threshold instensity for frequencies higher than a certain value and a gradual rise in threshold on the lower side of this "cut-off" frequency. The rate of rise in threshold with decreasing frequency depends markedly on the way the tones are delivered to the cochlea. The cut-off frequency varies from fiber to fiber; the fibers originating in the basal turn have a higher cut-off frequency and the fibers arising evidently in the upper turns have lower cut-off frequencies (cf. also 23).

Latency.—The responses of the basal turn fibers to clicks or to high-frequency pips (recorded in the lower part of the modiolus) start at or near the peak of the main (N_1) spike of the auditory nerve trunk. The response of the basal turn fibers to low frequency (e.g., 500 c.p.s.) tone pips are roughly synchronous to the nerve trunk responses recorded after cancellation of the microphonics. The fibers from the upper turns respond to low frequency tones at different latencies. These facts indicate that the neural responses recordable with gross electrodes represent synchronized discharges in the basal turn fibers.

Temporal relation between the phase of the applied tone and impulses.—

With low frequency tones, the action potentials of single fibers show a clear tendency to appear at a definite phase of the applied sound wave. This tendency is obscure for frequencies higher than 2000 c.p.s.

Multiple response.—In response to clicks or to short tone pips, an auditory nerve fiber discharges multiple responses as a rule. The second impulses in this repetitive discharge make a more-or-less synchronized volley in the auditory nerve. This is the origin of the second spike (so called N_2) of the nerve trunk action potential. [For the previously accepted view as to the origin of the N_2 spike, cf. (21, 98)]. A clear sign of initiation of multiple responses in the cochlea has been obtained by a pair of differential electrodes inserted in the basal turn [Davis, Tasaki & Goldstein (26), Figs. 5 and 6, left].

The time of initiation of nerve impulses relative to microphonic response.—With low frequency tones (290 and 500 c.p.s.), it was found that afferent impulses are initiated slightly before the peak of depolarization of the hair-bearing ends of the hair-cells. The local circuit resulting from this depolarization appears to be related to the initiation of impulses at the nerve terminals. This view is supported by the experiment demonstrating a great increase in responsiveness of the auditory nerve by a polarizing current flowing outwards through the surface membrance of the hair-cells near their nerve terminals (114).

In a series of unpublished experiments, the present reviewer has confirmed, in collaboration with Galambos, that these conclusions drawn from the observations on the guinea pig cochlea are applicable to the cat's ear. Introducing submicroscopic microelectrodes into the cochlear nerve near its origin in the medulla, responses of individual auditory nerve fibers were investigated. The shape of the response area and other properties of the fibers were very similar to those described above. The rate of threshold rise around the cut-off frequency was 20 to 25 db for a 10 per cent change in frequency at about 1000 c.p.s. and was much greater at higher frequencies. Immediately below this cut-off frequency, the threshold remained constant within 10 db for a change in frequency of 30 per cent.

The sharpness of the high frequency cut-off in the response-area for a single auditory nerve fiber may deserve some comment. The corresponding cut-off both in the mechanical movement of the cochlear partition [Békésy (4)] and in the amplitude of the microphonic response recorded in the upper turns of the cochlea [Tasaki *et al.* (113)] is by no means as sharp as the cut-off in the single fiber response-area. Since the microphonic response can spread in the cochlea to some extent, it is possible that the observed cut-off in the microphonics is less sharp than the cut-off of the local excitatory process. Békésy (9) describes a complex mechanical motion of the cochlear partition near the point of maximum vibration. The abrupt transition in the vibration pattern in this area seems to be related to the sudden loss of the excitatory effect of the traveling wave.

Auditory Pathway and Cortex

When a brief sound stimulus is delivered to a cat, the first sign of arrival of nerve impulses from the ear appears in the cortex approximately 10 msec. after the start of the microphonics in the cochlea. Recent macro- and microelectrode studies indicate that the latencies of responses to a strong click stimulus at various nuclei along the main auditory pathway are: cochlear nuclei, 1.5 to 2 msec.; superior olivary complex, approx. 4 msec; inferior colliculus (117), 6 to 9 msec.; medial geniculate body (52, 47), 7 to 10 msec.; and auditory cortex (84) 8 to 12 msec. (cf. also 95).

The behavior of the nerve impulses in the auditory pathway is determined undoubtedly by the processes of excitation and inhibition at the synapses in these nuclei. The laws governing the properties of these synapses are probably common to all other neurones in the central nervous system. The main difficulty in electrophysiological studies of the auditory pathways and nuclei appears to lie in the anatomical complexity of the central nervous system.

Cochlear nuclei.—An unsuccessful attempt was made by Tasaki & Davis (111) to reproduce, on the cochlear nucleus of the guinea pig, Galambos' previous observation on the inhibition of impulse discharges by sound stimuli (43). Single unit discharges picked up by submicroscopic glass-pipette electrodes inserted in the medulla near the origin of the eighth nerve could not be suppressed by sound. Some of the units responded to short tone pips with a long latency; they were apparently second-order neurones in the auditory system. The response-areas of these elements were not much different from those of the first-order neurones discussed in the preceding section. At present the reason for this failure in demonstrating inhibition is at least partly clear on the follow grounds.

It is known that many of the nerve cells in the ventral cochlear nucleus have practically no dendrites while the cell bodies in the dorsal cochlear nucleus are provided with well-developed dendrites [e.g., Krieg, (76)]. Cell bodies with long dendrites can develop a large potential field around them (115), but a cell body without any dendrite cannot generate an external potential field when its surface is uniformly activated. Microelectrodes larger than 1μ at the tip pick up only the external potential field, while submicroscopic (smaller than 0.5μ) electrodes can record intracellular potentials as well as external fields.

In the experiment by Tasaki & Davis records were taken in most cases from nerve fibers in the ventral cochlear nucleus. In Galambos' experiment, on the contrary, the large microelectrode selectively recorded the potentials from cell bodies with well-developed dendrites. In unpublished experiments Galambos & Tasaki observed suppression of spontaneous discharges with submicroscopic electrodes inserted into the dorsal cochlear nucleus of the cat.

Superior olivary region.—The third-order neurones in the auditory pathway start in the superior olivary nuclear mass which consists of at least five

major subdivisions [cf. Galambos, (45) p. 506]. Using Ringer-filled 2μ electrodes, Hilali & Whitfield (56) examined the response-areas of individual elements in the nucleus of the trapezoid body (one of the subdivisions of the superior olivary nuclear mass). In the range of frequency higher than 300 c.p.s., each unit responded with a limited response-area, which was slightly broader than those reported by Galambos & Davis for the elements in the cochlear nucleus (46). They found also some units which responded to low frequency tones with extremely flat response-areas.

Inferior colliculus and medial geniculate body.—At the next higher level in the main auditory pathway, namely in the inferior colliculus, the microelectrode studies by Thurlow *et al.* (117) still appear to be the sole source of direct physiological information. At the next level, namely in the medial geniculate body, unitary responses have been recorded by Gross & Thurlow (52) and by Galambos and his associates (44, 94). This work has already been reviewed by Ades (1).

Auditory cortex.—Electric responses of the auditory cortex have been investigated so far only with gross recording electrodes. Using the strychnine-spike technique, Tunturi (126) extended his earlier work (123, 124) on the frequency localization in the middle ectosylvian area of the dog. As sound stimuli, he used tones whose amplitude was modulated by a probability curve.

> The use of such "probability pulses" of an adequate duration is the best compromise between the sharpness of the frequency distribution of the sound and the definitiveness of the time of delivery of the sound. If the duration of a "tone" is too short, its frequency spectrum becomes too wide and it is hard to speak of its frequency. [A sine wave with a sudden onset contains an infinite number of higher harmonics.] If the amplitude of a tone rises and falls too gradually, it is difficult to define the beginning and the end of the stimulus.

Using probability pulses, Tunturi determined the response areas of small groups of elements giving rise to strychnine spikes. He found, confirming his previous findings, that different spots on the ectosylvian gyrus have different effective frequency bands. The logarithm of the most sensitive frequency was found to shift as the linear distance on the cortex.

Hind (59) also used the method of evoked strychnine spikes in his study of the auditory cortex of the cat. In the middle ectosylvian gyrus, he found the orderly shift in the effective frequency band among a posterior-anterior axis. The anterior ectosylvian gyrus responded to low frequency tones. A high frequency area extended posteriorly across the posterior ectosylvian gyrus. A region on the pseudosylvian gyrus exhibited relatively wide response areas.

Using click stimuli and taking evoked potentials of the cat nonstrychnized cortex as an index, Mickle & Ades (83) showed that projection of the auditory, vestibular, and a part of the somatic system overlap extensively. These authors (84) further examined the time sequence of the spread of activity over the auditory cortex.

A very elegant method was employed by Lilly & Cherry (80) in their study of the spread of electric responses in the cat's auditory cortex. An array of 25 metal electrodes was placed on the surface of the cortex. Connecting all these electrodes to the same number of separate amplifiers and then to an array of 25 neon lamps, the time sequence of the explansion, and the subsequent skrinkage, of the responsive surface was pursued with a cinematograph camera. The edge of the active area was found to move at a velocity of about 1 m.per sec. or less. The neural mechanism determining this velocity of expansion of the active surface is still obscure.

Perl & Casby (88) were concerned with the spatial (volume conductor) spread of electric responses in the auditory cortex. They devised a set of metallic electrodes which is sensitive only to sinks or sources in the superficial layer of the cortex and found that the auditory area determined by this new method was more definitive than that obtained by a unipolar recording electrode.

Pribram, Rosner & Rosenblith (91) examined in monkeys the extent of the cortical area responding to click stimuli and found that a larger area was activated than had hitherto been described. They suggested that the response to click stimuli recorded from the parietal cortex was mediated by collaterals which branch from the main projection and connect the medial geniculate nucleus with the cortex of the supratemporal plane. Previous experimenters, who mapped out the responsive area, frequently resected the inferior portion of the frontal and parietal lobe in order to expose the temporal lobe. This procedure, they pointed out, may cause retrograde degeneration in cells in the geniculate and reduce the extent of the responsive area.

Rosner & Heise (97) investigated the effect of anesthesia upon the frequency threshold curve in the cat cortex. Contrary to the author's contention, the present reviewer received the impression from their data that, during the course of progress of a lethal dose of anesthesia, the shape of the frequency threshold curve changed only slightly.

In a recent preliminary report, Sumi, Katsuki & Uchiyama (107) mentioned that they recorded unitary responses at four different levels in the auditory tract.

Other Developments

Behavioral responses.—Schuknecht (100) described the details of the technique for studying the cochler function by the method of conditioned responses in experimental animals. Neff & Hind (87) determined the auditory threshold of the cat by this method. Hind & Schuknecht (60) compared the auditory threshold of the cat determined by behavioral tests with that obtained by the strychnine spike method. Schuknecht & Sutton (101, 108) examined the hearing loss in the cat by the behavioral and cortical methods after local injuries in various parts of the cochlea. Alexander *et al.* (2) investigated the hearing loss caused by "selective" cochlear destructions by

the behavioral method. Evarts (35) and Tunturi (125) examined the effect of cortical lesions on hearing.

Psychophysical investigations.—There is a large volume of publications dealing with psychophysical phenomena related to hearing; this topic has recently been reviewed by Licklider (79), Egan (31), and Hirsh (61). These articles may roughly be divided into (*a*) a group dealing with pitch preception for pure tones (54, 64, 106), for tone-pips or amplitude-modulated tones (104, 118), (*b*) a group of papers dealing with auditory fatigue and sensitization (20, 32, 33, 55, 62, 63, 65, 68, 119), (*c*) articles on the effect of white noise (86, 109, 128), (*d*) experiments on localization of a sound source (102, 103), and others.

Vestibular system and cerebellum.—Lowenstein (82) examined the effect of galvanic polarization on the impulse discharge from sensory endings in the isolated labyrinth of the thornback ray. Hallpike & Hood (53) investigated the function of the semicircular canals in man by taking an after-sensation following an angular acceleration of the head as an index. Timm & Müller (120) emphasized the importance of the force acting directly on the cupula itself (because of its greater specific gravity), together with the force caused by the streaming of the endolymph, as the adequate stimulus to the human semicircular canals. Van Eyck and Gernandt (127) studied reflex movements of the pigeon wing muscles in response to vestibular stimulation. Bornschein & Schubert (18) investigated the vestibular Coriolis effects in guinea pigs and in man. Several articles were published dealing with the vestibular nuclei and the cortical projection of the vestibular system (3, 83, 85, 116). Gernandt (48) and Gernandt & Thulin (49) demonstrated that the spontaneous impulse discharge in the eighth nerve and adequate vestibular stimulation exert a facilitatory or inhibitory effect upon the spinal cord reflexes.

Bremer & Gernandt (19) recorded responses of the cat's cerebellar cortex to click stimuli with extracellular microelectrodes. They presented evidence that these responses are summated discharges of the large Purkinje cells.

Middle ear and bone conduction.—Wever and his associates (135 to 138) continued their studies on conduction of sound waves through the middle ear using the microphonics at the sound window as the main tool. Ranke *et al.* (92) examined the phase relation between the applied sound wave and the cochlear microphonics at the round window of the guinea pig. Totsuka *et al.* (122) investigated the reflex contraction of the auricular and intra-aural muscles. Benson & Eldredge (15) measured, with a probe-tube microphone, the sound pressure in front of the ear drum under various experimental conditions. Franke *et al.* (41) examined the effect of jaw motions upon hearing by bone conduction. Goodhill & Holcomb (51) employed cochlear microphonics in the cat for evaluation of bone conduction. Fournier (40) and Zwislocki (140, 141) investigated the physical nature of bone donduction.

Acoustic trauma.—Injurious effects produced in the cochlea by acoustic over-stimulation were investigated by Davis *et al.* (24), Rüedi (99), Bornschein & Krejci (16), by Wever & Lawrence (133), and by many others.

Miscellaneous problems related to hearing.—DeVries *et al.* (29, 69) reported on nonlinear microphonic responses of the lateral line of a fish. Previously he discussed Brownian motion at the ear drum (28). Legouix *et al.* (77, 78) and Katsuki & Davis (71) described their observations on the cochlea of a desert rodent which was found to have both the cochlear and the vestibular portions of the labyrinth exposed in the bulla.

Rasmussen (93) published the results of his further observations on the olivocochlear bundle. This bundle consists of small myelinated nerve fibers arising from cell-bodies in the olivary complex in the medulla and terminating in the cochlea. Because of their anatomical arrangment of the fibers and the cell-bodies, these fibers have been inferred to be efferent in nature. Portmann & Portmann (90) supported this view and Galambos (by personal communication) has some evidence indicating that electric stimulation of these fibers may inhibit impulse discharges in the primary neurones. It is not easy to stimulate these fibers selectively without exciting many other fibers in the medulla. So far no attempt has been reported to record impulses in these fibers in their pathway between the medulla and cochlea.

Flotlorp (39) investigated the mechanism of electrophonic hearing (sensation of sound caused by alternating currents applied to the human ear). Keidel (73) examined the process of initiation of nerve impulses in the skin of the frog by vibration. Keidel *et al.* (72, 74) measured the threshold for vibratory sensation as well as some dynamic properties of the human skin. Békésy (13) studied vibratory senses in the human skin as a model of the cochlea.

LITERATURE CITED

1. Ades, H. W., *Ann. Rev. Physiol.*, **16**, 391–402 (1954)
2. Alexander, I. E., Githler, F. J., Deiss, A., and Radwin, H. M., *Arch. Otolaryngol.*, **61**, 46–53 (1955)
3. Anderson, S., and Gernandt, B. E., *Acta Oto-Laryngol.* Suppl. 116, 303 pp. (1954)
4. Békésy, G. v., *J. Acoust. Soc. Amer.*, **21**, 233–45 (1949)
5. Békésy, G. v., *J. Acoust. Soc. Amer.*, **23**, 18–28 (1951)
6. Békésy, G. v., *J. Acoust. Soc. Amer.*, **23**, 29–35 (1951)
7. Békésy, G. v., *J. Acoust. Soc. Amer.*, **24**, 72–76 (1952)
8. Békésy, G. v., *J. Acoust. Soc. Amer.* **24**, 399–409 (1952)
9. Békésy, G. v., *J. Acoust. Soc. Amer.*, **25**, 770–85 (1953)
10. Békésy, G. v., *J. Acoust. Soc. Amer.*, **25**, 786–90 (1953)
11. Békésy, G. v., *Ann. Otol. Rhinol. & Laryngol.*, **63**, 448–68 (1954)
12. Békésy, G. v., *J. Acoust. Soc. Amer.*, **27**, 137–45 (1955)
13. Békésy, G. v., *J. Acoust. Soc. Amer.*, **27**, 830–41 (1955)
14. Békésy, G. v., and Rosenblith, W. A., *Handbook of Psychology*, Chap. 27, 1075–1115 (John Wiley and Sons, New York, N. Y., 1436 pp. 1951)
15. Benson, R. W., and Eldredge, D. H., *J. Acoust. Soc. Amer.*, **27**, 373–75 (1955)
16. Bornschein, H., and Krejci, F., *Experientia*, **9**, 69–70 (1953)
17. Bornschein, H., and Krejci, F., *Acta Oto-Laryngol.*, **45**, 467–78 (1955)
18. Bornschein, H., and Schubert, G., *Z. Biol.*, **107**, 95–107 (1954)
19. Bremer, F., and Gernandt, B. E., *Acta Physiol. Scand.*, **30**, 120–36 (1954)
20. Carterette, E. C., *J. Acoust. Soc. Amer.*, **27**, 103–11 (1955)
21. Davis, H., *Handbook of Psychology*, Chap. 28, 1116–42 in (John Wiley and Sons, New York, N. Y., 1436 pp. 1951).
22. Davis, H., *Nerve Impulse*, 58–139 (Josiah Macy, Jr. Foundation, New York, N. Y., 224 pp. 1953)
23. Davis, H., *Ann. Oto. Rhinol. & Laryngol.*, **63**, 469–80 (1954)
24. Davis, H., and associates, *J. Acoust. Soc. Amer.*, **25**, 1180–89 (1953)
25. Davis, H., Fernandez, C., and McAuliffe, D., *Proc. Nat. Acad. Sci.* (U.S.), **36**, 580–87 (1950)
26. Davis, H., Tasaki, I., and Goldstein, R., *Cold Spring Harbor Symp. Quant. Biol.*, **17**, 143–54 (1952)
27. Davis, H., Tasaki, I., Smith, C. A., and Deatherage, B. H., *Federation Proc.*, **14**, (1) 112 (1955)
28. DeVries, H., *J. Acoust. Soc. Amer.*, **24**, 527–33 (1952)
29. DeVries, H., Kuiper, J. W., and Ubbens, D. R., *Nature*, **175**, (4452) 383–84 (1955)
30. Diestel, H. G., *Acustica*, **4**, 489–99 (1954)
31. Egan, J. P., *Ann. Rev. Psychol.*, **5**, 89–110 (1954)
32. Egan, J. P., *J. Acoust. Soc. Amer.*, **27**, 111–20 (1955)
33. Egan, J. P., *J. Acoust. Soc. Amer.*, **27**, 737–40 (1955)
34. Engström, H., and Wersäll, J., *Ann. Otol. Rhinol. & Laryngol.*, **62**, 507–12 (1953)
35. Evarts, E. V., *J. Neurophysiol.*, **15**, 443–48 (1952)
36. Fernández, C., *J. Acoust. Soc. Amer.*, **24**, 519–23 (1952)
37. Fernández, C., *Ann. Otol. Rhinol. & Laryngol.*, **64**, 1193–1203 (1955)
38. Fletcher, H., *J. Acoust. Soc. Amer.*, **24**, 129–31 (1952)
39. Flottorp, G., *J. Acoust. Soc. Amer.*, **25**, 236–45 (1953)

40. Fournier, J. E., *Ann. Otolaryngol.*, **70**, 401–33 (1955) cited in Excerpta Medica XI, **7**, 1566 (1954)
41. Franke, E. K., von Gierke, E., Grossman, F. M., and von Wittern, W. W., *J. Acoust. Soc. Amer.*, **24**, 142–46 (1952)
42. Gacek, R. R., and Rasmussen, G. L., (In preparation)
43. Galambos, R., *J. Neurophysiol.*, **7**, 287–303 (1944)
44. Galambos, R., *J. Neurophysiol.*, **15**, 381–400 (1952)
45. Galambos, R., *Physiol. Rev.*, **34**, 497–528 (1954)
46. Galambos, R., and Davis, H., *J. Neurophysiol.*, **6**, 39–58 (1943)
47. Galambos, R., Rose, J. E., Bromiley, R. B., and Hughes, J. R., *J. Neurophysiol.*, **15**, 359–80 (1952)
48. Gernandt, B., *Acta Physiol. Scand.*, **27**, 169–82 (1953)
49. Gernandt, B. E., and Thulin, C.-A., *Amer. J. Physiol.*, **172**, 653–60 (1953)
50. Goldstein, R., *Amer. J. Physiol.*, **178**, 331–37 (1954)
51. Goodhill, V., and Holcomb, A. L., *Ann. Otol. Rhinol. & Laryngol.*, **64**, 1212–33 (1955)
52. Gross, N. B., and Thurlow, W. R., *J. Neurophysiol.*, **14**, 409–22 (1951)
53. Hallpike, C. S., and Hood, J. D., *Proc. Roy. Soc. B.*, **141**, 542–61 (1953)
54. Harris, J. D., *J. Acoust. Soc. Amer.*, **24**, 750–55 (1952)
55. Harris, J. D., and Rawnsley, A. I., *J. Acoust. Soc. Amer.*, **25**, 760–64 (1953)
56. Hilali, S., and Whitfield, I. C., *J. Physiol.*, **122**, 158–71 (1953)
57. Hilding, A. C., *Ann. Otol. Rhinol. & Laryngol.*, **61**, 354–70 (1952)
58. Hilding, A. C., *Ann. Otol. Rhinol. & Laryngol.*, **64**, 278–90 (1955)
59. Hind, J. E., *J. Neurophysiol.*, **16**, 475–89 (1953)
60. Hind, J. E., and Schuknecht, H. F., *J. Acoust. Soc. Amer.*, **26**, 89–97 (1954)
61. Hirsh, I. J., *Ann. Rev. Psychol.*, **7**, 95–118 (1955)
62. Hirsh, I. J., and Bilger, R. C., *J. Acoust. Soc. Amer.*, **27**, 1186–94 (1955)
63. Hirsh, I. J., and Ward, W. D., *J. Acoust. Soc. Amer.*, **24**, 131–41 (1952)
64. Huggins, W. H., *J. Acoust. Soc. Amer.*, **24**, 582–89 (1952)
65. Hughes, J. R., *J. Acoust. Soc. Amer.*, **26**, 1064–70 (1954)
66. Jensen, C. E., and Vilstrup, T., *Acta Chem. Scand.*, **8**, 399–401 (1954)
67. Jensen, C. E., and Vilstrup, T., *Acta Chem. Scand.*, **8**, 697–98 (1954)
68. Jerger, J. F., *J. Acoust. Soc. Amer.*, **27**, 121–24 (1955)
69. Jielof, R., Spoor, A., and DeVries, H., *J. Physiol.*, **116**, 137–57 (1952)
70. Katsuki, Y., and Covel, W. P., *Laryngoscope*, **63**, 1–17 (1953)
71. Katsuki, Y., and Davis, H., *J. Neurophysiol.*, **17**, 308–16 (1954)
72. Keidel, W. D., *Pflügers Arch. ges. Physiol.*, **256**, 242–64 (1952)
73. Keidel, W. D., *Pflügers Arch. ges. Physiol.*, **260**, 416–36 (1955)
74. Keidel, W. D., and Schmitt, H. G., *Pflügers Arch. ges. Physiol.*, **260**, 274–91 (1955)
75. Keidel, W. D., and Sick, L., *Z. Biol.*, **105**, 443–53 (1953)
76. Krieg, W. J. S., *Functional Neuroanatomy* (The Blakiston Co., New York, N. Y., 659 pp. 1953)
77. Legouix, J. P., Peter, F., and Wisner, A., *Mammalia*, **18**, 262 (1954)
78. Legouix, J. P., and Wisner, A., *Acustica*, **5**, 208–16 (1955)
79. Licklider, J. C. R., *Ann. Rev. Psychol.*, **4**, 89–110 (1953)
80. Lilly, J. C., and Cherry, R. B., *J. Neurophysiol.*, **17**, 521–32 (1954)
81. Ling, G., and Gerard, R. W., *J. Cell. Comp. Physiol.*, **35**, 39–73 (1949)
82. Lowenstein, O., *J. Physiol.*, **127**, 104–17 (1955)
83. Mickle, W. A., and Ades, H. W., *Amer. J. Physiol.*, **170**, 682–89 (1952)

84. Mickle, W. A., and Ades, H. W., *J. Neurophysiol.*, **16**, 608–33 (1953)
85. Mickle, W. A., and Ades, H. W., *Amer. J. Physiol.*, **176**, 243–46 (1954)
86. Mowbray, G. H., Gebhard, J. W., and Byham, C. L., *J. Acoust. Soc. Amer.*, **28**, 106–10 (1956)
87. Neff, W. D., and Hind, J. E., *J. Acoust. Soc. Amer.*, **27**, 481–83 (1955)
88. Perl, E. R., and Casby, J. U., *J. Neurophysiol.*, **17**, 429–42 (1954)
89. Peterson, L. C., and Bogert, B. P., *J. Acoust. Soc. Amer.*, **22**, 369–81 (1950)
90. Portmann, M., and Portmann, C., A.M.A. *Arch. Otolaryngol.*, **59**, 543–54 (1954)
91. Pribram, K. H., Rosner, B. S., and Rosenblith, W. A., *J. Neurophysiol.*, **17**, 336–44, (1954)
92. Ranke, O. F., Keidel, W. D., and Weschke, H. G., *Z. Biol.*, **105**, 380–92 (1953)
93. Rasmussen, G. L., *J. Comp. Neurol.*, **99**, 61–74 (1953)
94. Rose, J. G., and Galambos, R., *J. Neurophysiol.*, **15**, 343–58 (1952)
95. Rosenblith, W. A., *Ann. Otol. Rhinol. & Laryngol.*, **63**, 839–60 (1954)
96. Rosenblith, W. A., and Rosenzweig, M. R., *J. Acoust. Soc. Amer.*, **23**, 583–88 (1951)
97. Rosner, B., and Heise, G. A., *J. Acoust. Soc. Amer.*, **26**, 1077–78 (1954)
98. Rosenzweig, M. R., and Rosenblith, W. A., *Psychol. Monographs*, **67** (13), No. 363, 26 pp. (1953)
99. Rüedi, L., *Ann. Otol. Rhinol. & Laryngol.*, **63**, 703–26 (1954)
100. Schuknecht, H. F., *Arch. Otolaryngol.*, **58**, 377–97 (1953)
101. Schuknecht, H. F., and Sutton, S., *Arch. Otolaryngol.*, **57**, 129–42 (1953)
102. Skramlik, E. v., *Z. Biol.*, **106**, 239–84 (1953)
103. Skramlik, E. v., *Z. Biol.*, **107**, 241–51 (1954)
104. Small, A. M., Jr., *J. Acoust. Soc. Amer.*, **27**, 751–60 (1955)
105. Smith, C. A., Lowry, O. H., and Wu, M. L., *Laryngoscope*, **64**, 141–53 (1954)
106. Strange, P. H., *J. Physiol.*, **129**, 225–36 (1955)
107. Sumi, T., Katsuki, Y., and Uchiyama, H., *Proc. Japan. Acad.*, **32**, 67–71 (1956)
108. Sutton, S., and Schuknecht, H. F., *Ann. Otol. Rhinol. & Laryngol.*, **63**, 727–53 (1954)
109. Symmes, D., Chapman, L. F., and Halstead, W. C., *J. Acoust. Soc. Amer.*, **27**, 470–73 (1955)
110. Tasaki, I., *J. Neurophysiol.*, **17**, 97–122 (1954)
111. Tasaki, I., and Davis, H., *J. Neurophysiol.*, **18**, 151–58 (1955)
112. Tasaki, I., Davis, H., and Eldredge, D. H., *J. Acoust. Soc. Amer.*, **26**, 765–73 (1954)
113. Tasaki, I., Davis, H., and Legouix, J. P., *J. Acoust. Soc. Amer.*, **24**, 502–19 (1952)
114. Tasaki, I., and Fernández, C., *J. Neurophysiol.*, **15**, 497–512 (1952)
115. Tasaki, I., Polley, E. H., and Orrego, F., *J. Neurophysiol.* **17**, 454–74 (1954)
116. Thulin, C.-A., *Acta Physiol. Scand.*, **28** Suppl. 103, 61 pp. (1953)
117. Thurlow, W. R., Gross, N. B., Kemp, E. H., and Lowy, K., *J. Neurophysiol.*, **14**, 289–304 (1951)
118. Thurlow, W. R., and Small, A. M., Jr., *J. Acoust. Soc. Amer.*, **27**, 132–37 (1955)
119. Thwing, E. J., *J. Acoust. Soc. Amer.*, **27**, 741–48 (1955)
120. Timm, C., and Müller, H., *Experientia*, **9**, 148–49 (1954)
121. Tonndorf, J., Hyde, R. W., and Brogan, F. A., *Ann. Otolaryngol.*, **64**, 392–405 (1955)
122. Totsuka, G., Nakamura, K., and Kirikae, I., *Ann. Otol. Rhinol. & Laryngol.*, **63**, 939–49 (1954)
123. Tunturi, A. R., *Amer. J. Physiol.*, **162**, 489–502 (1950)

124. Tunturi, A. R., *Amer. J. Physiol.*, **168**, 712–27 (1952)
125. Tunturi, A. R., *Amer. J. Physiol.*, **181**, 225–29 (1955)
126. Tunturi, A. R., *Amer. J. Physiol.*, **181**, 630–38 (1955)
127. Van Eyck, M., and Gernandt, B. E., *Acta Oto-Laryngol.*, **43**, 526–28 (1953)
128. Webster, J. C., Miller, P. H., Thompson, P. O., and Davenport E. W., *J. Acoust. Soc. Amer.*, **24**, 147–52 (1952)
129. Wever, E. G., *Theory of Hearing* (John Wiley and Sons, New York, 1949)
130. Wever, E. G., and Lawrence, M., *Proc. Nat. Acad. Sci.*, U.S. **38**, 133–38 (1952)
131. Wever, E. G., and Lawrence, M., *Ann. Otol. Rhinol. & Laryngol.*, **61**, 824–35 (1952)
132. Wever, E. G., and Lawrence, M., *Physiological Acoustics* (Princeton University Press, Princeton, N. J., 454 pp., 1954)
133. Wever, E. G., and Lawrence, M., *J. Acoust. Soc. Amer.*, **27**, 853–58 (1955)
134. Wever, E. G., Lawrence, M., and Békésy, G. v., *Proc. Nat. Acad. Sci.* U. S. **40**, 508–10 (1954)
135. Wever, E. G., Lawrence, M., and Rahm, W. E. Jr., *Proc. Nat. Acad. Sci.* U. S. **40**, 209–18 (1954)
136. Wever, E. G., and Vernon, J. A., *Acta Otolaryngol.*, **45**, 433–39 (1955)
137. Wever, E. G., and Vernon, J. A., *Ann. Otol. Rhinol. and Laryngol.*, **65**, 5–14 (1956)
138. Wever, E. G., Vernon, J. A., and Lawrence, M., *Ann. Otol. Rhinol. & Laryngol.*, **64**, 383–91 (1955)
139. Zwislocki, J., *J. Acoust. Soc. Amer.*, **25**, 743–51 (1953)
140. Zwislocki, J., *J. Acoust. Soc. Amer.*, **25**, 986–89 (1953)
141. Zwislocki, J., *J. Acoust. Soc. Amer.*, **25**, 752–59 (1953)
142. Zwislocki, J., *Symp. Physiol. Psychol.* (ONR Symp. Report ACR-1, 182–90 1955)

PITUITARY AND ADRENAL GLANDS[1,2]

By B. T. Donovan and G. W. Harris

Department of Neuroendocrinology, Institute of Psychiatry, British Postgraduate Medical Federation, London University, London, England

This review is mainly concerned with work on the regulation of anterior pituitary and adrenal cortical function and with the interrelationships between the pituitary-adrenal and pituitary-thyroid axes. Some books and numerous reviews dealing with these topics have appeared during the last year. Volume III of *The Hormones* (1) includes reviews on pituitary and steroid hormones together with an article by Noble (2) on the physiology of the adrenal cortex. The proceedings of a colloquium held by the Ciba Foundation on the human adrenal cortex includes thirty-five papers and reviews (3). Hypothalamo-hypophysial interrelationships are dealt with in a publication of the Houston Neurological Society (4), in a monograph by Harris on the neural control of the pituitary gland (5), and in a similar publication by Bargmann (6). The *Fifth Annual Report on Stress* contains reviews by von Euler on stress and catechol hormones (7), Gray *et al.* on adrenal influences upon the stomach (8), Nelson on the factors affecting adrenocortical secretion (9), Scharrer on neurosecretion (10) and by Ingle on the role of the adrenal cortex in the aetiology of disease (11). The mechanism of stimulation of adrenocorticotropic hormone (ACTH) secretion has been surveyed by Munson & Briggs (12), whilst Cleghorn (13, 14) has reviewed the interrelationships between the nervous and endocrine systems. Reviews on the secretion and on the clinical aspects of the adrenal cortex (16, 17, 18) and on the physiology and medical importance of aldosterone (19 to 22) have been published. The relationship between the endocrine system and neoplastic disease has also been discussed (23, 24, 25). The biochemistry and physiology of neurohypophysial hormones have been dealt with by van Dyke, Adamsons & Engel (26).

Anatomy

Few fundamental observations upon the anatomy of the hypothalamo-hypophysial system have been made recently; work has been devoted more to filling gaps in present knowledge of this system. The old question as to whether the hypothalamus regulates anterior pituitary activity by a direct nerve supply to the *pars distalis* has been raised by the description of Metuzals (27) of "nerve fibres" in the gland of the duck. However, it should be pointed out once again that the vagaries of silver stains make it difficult

[1] The survey of literature pertaining to this review was concluded July 15, 1956.

[2] The following abbreviations are used in this review: ACTH (adrenocorticotropic hormone); FSH (follicle stimulating hormone); LH (luteinizing hormone); TSH (thyroid stimulating hormone); ADH (antidiuretic hormone).

to differentiate precisely between nerve fibres and reticular fibres in the gland and should necessitate the control procedure in staining sections from normal and "denervated" glands on the same slide. Further emphasis is placed on this point by the failure of the electron microscope to reveal nerve fibres in the anterior pituitary gland [Palay (28), Farquhar & Rinehart (29)], although reticular fibres are clearly seen. Okada, Ban & Kurotsu (30) failed to find nerve fibres in the *pars distalis* using ordinary staining methods.

The view expressed by Long (31) concerning the mechanism of anterior pituitary regulation is generally accepted. "It is agreed that the anterior pituitary is devoid of secretory nerve fibres and that therefore the mechanisms of secretion must be attributed to humoral factors that reach the gland through its blood supply." One component of this blood supply upon which attention has been focussed is the hypophysial portal system of the pituitary. In confirmation of earlier observations by other workers on amphibia and rats, Worthington (32) has shown that the blood flow in the portal vessels of the mouse is from the capillaries in the median eminence of the tuber cinereum to the sinusoids of the *pars distalis*. He observed that the rate of flow in this system could be altered by parenteral or local administration of such compounds as epinephrine and methacholine chloride. These findings are compatible with the view that the anterior pituitary gland is under neurohumoral control by the hypothalamus, viz., that nerve fibres in the hypothalamus liberate some humoral agent(s) into the portal vessels whereby this substance is carried to the *pars distalis* to affect the activity of the gland. The vascular architecture of the region has been studied by several workers (33, 34, 35) who have confirmed the previous findings of Finley, Horne Craigie and others regarding the rich vascularization of the supraoptic and paraventricular nuclei. Engelhardt (34) paid particular attention to the origin of the vessels forming the primary plexus of the portal system, and agrees with earlier workers that these vessels originate from the plexus in the *pars tuberalis*. The area of necrosis in the *pars distalis* of the rat, which follows cauterisation of the portal vessels of the stalk, has been studied by Daniel & Prichard (36). They believe that the human condition of "postpartum necrosis of the anterior pituitary" is due to a severe impairment of the circulation in the vessels of the hypophysial stalk and lower infundibular stem. Brettschneider (37) has added details regarding the innervation of the primary plexus in the infundibulum, and believes that the vessels of this plexus come into close relationship with both hypothalamic and peripheral autonomic fibres. Gregoretti (38) investigated the anatomy of the accessory supraoptic nuclei in man.

The possibility that anterior lobe hormones pass to the neurohypophysis and hypothalamus to influence some hypothalamic nerve "centre" has been investigated by Leonhardt (39) who attempted to trace the pathway of trypan blue in the intravital staining of the neurohypophysis. He concludes

that such stains pass from the blood to the adenohypophysis and from there to the neural lobe, pituitary stalk and hypothalamus, and that a similar path could be utilized by the physiological products of the adenohypophysis. This conclusion is in accord with that of Gaupp & Spatz (40) derived from an experimental study of pituitary stalk-section in the rabbit. The opposite and more likely hypothesis, that substances originating in the hypothalamus (e.g., neurosecretory material) pass via the portal vessels to the anterior lobe of the pituitary and there influence the activity of this gland, has received more attention since this has been suggested as a possible mechanism controlling ACTH secretion. This concept has been discussed by Scharrer (10) and Hild (41) and will be examined in more detail below. Contributions from Japan (30) and Sweden (42) describe the neurosecretory system in the frog, rabbit, and wolf. Their observations in the rabbit led Okada, Ban & Kurotsu (30) to conclude that neurosecretory material may reach the *pars distalis* via the portal vessels, perivascular spaces or through the *pars intermedia*, and that this could form the pathway of hypothalamic control over the adenohypophysis. However Green and van Breemen (43), after studying the neurosecretory material in the hypothalamus and pituitary gland of the rat, cat, and Virginian opossum with the electron microscope, raise points of an equivocal nature regarding the origin of neurosecretion in the neurohypophysis. There is little doubt that Gomori-stainable material in the neurohypophysis is depleted by noxious stimuli that simultaneously evoke increased discharge of ACTH. Rothballer (44) finds the material is depleted by adrenalectomy, pain, restraint, noise, and even by placement in unfamiliar surroundings. Ether anaesthesia resulted in loss of the stainable material, although anaesthesia with chloroform, pentobarbital, or chloralose was without effect. Once anaesthesia had been induced, the depletion which normally follows pain or osmotic stimuli was blocked. In addition Rothballer illustrates a vasodilatation of pituitary blood vessels following a painful stress. Shibusawa *et al.* (45) also record a loss of neurosecretory material following laparotomy in the dog, but Imai (46) noted only minor changes following enucleation of the eyes in rats.

The cellular site of origin of the anterior pituitary hormones continues to be a controversial topic, particularly with regard to the source of ACTH. One difficulty in this connection arises from the fact that ACTH appears to be a simple protein and may not be differentially detectable histochemically. The glycoprotein pituitary hormones, FSH, LH, and TSH, on the other hand, can be demonstrated by the periodic acid-Schiff (PAS) technique, and the application of this method has led to considerable advances in our knowledge of pituitary cytology. Thus Purves & Griesbach (47) have been able to show that the "gonadotrophs" tend to be clustered around the terminal branches of the portal vessels on the lower surface of the rat pituitary, whilst "thyrotrophs" occupy a more central position in the gland. Both cell types were described as PAS positive basophiles. More recent work

(48) has indicated that the FSH-secreting cells are situated peripherally and the LH-producing cells more centrally in the gland. Support for a basophilic cell origin of gonadotrophins and TSH comes from the studies of Jubb and McEntee (49) on the bovine gland and Siegel (50) in the bat. The cytological changes in the rat anterior pituitary from birth to maturity were examined by Siperstein *et al.* (51) who found that whilst degranulation of basophilic gonadotrophs occurred at puberty and the aldehyde-fuchsin staining thyrotrophs could be recognized from birth onwards, ACTH-secreting cells could not be identified.

Conflicting findings on the effect of stress on the *pars distalis* underline present uncertainty on the source of ACTH. Knigge (52) observed the effect of stress (immersion in water at 70°C.) on intact and thyroidectomized rats. He recorded that in intact animals the acidophil and argyrophil cells increased in number whilst beta and delta type basophils were not altered significantly. After thyrodectomy beta basophils were reduced in number together with hypertrophy and vacuolization of the delta basophils and no change in the argyrophils. Since the only change noted on stressing the thyroidectomized rat was an increase in argyrophil cells it was concluded that these cells produced ACTH. This work has since been repeated by Timmer & Finerty (53) who found that the percentage of acidophils, basophils, or chromophobes one, three or twelve hours after stress was not altered although a fall in pituitary weight due to a loss of both solid and fluid matter was recorded. The latter results accord with those of Halmi & Bogdanove (54, 55) who compared the ACTH content of the hypophyses of rats following thyroidectomy, oestrogen treatment or castration with the cytological picture and could find no correlation between the assayable potency of the gland and the number or degree of granulation of the chromophils. Knigge (56) has since communicated the results of a cytological study combined with assay of the hormone content of the hypophysis and now believes that the delta basophils secrete ACTH and (57) that the argyrophil cells are gonadotrophs. A basophilic origin of this hormone is in accord with the changes which occur in Cushing's syndrome and Addison's disease. The human gland has recently been studied by Currie & Symington (58) who report that a degranulation of the basophils occurred during stress with recovery under chronic conditions. Russfield (59) suggests that amphophil cells of the human pituitary may be responsible for secreting ACTH, gonadotrophic hormone and growth hormone as well as TSH. An important question in these studies concerns any relationship between the intensity of staining of a cell and its hormone content. It seems possible that a cell which is actively secreting may have a low content and show only weak staining properties. Del Conte & Stux (60) studied the thyrotrophs (aldehyde-fuschsin stain) of the rat hypophysis and made simultaneous assays of the blood TSH content under various experimental conditions. They found that the intensity of the stain in the thyrotrophs varied inversely with the hormone concentration in the blood.

Maturation of the Pituitary-Adrenal Axis

The relationship between the foetal and maternal adrenocortical systems has been the subject of several investigations. From studies of the effects of decapitation of rat foetuses it is known that the secretion of ACTH has begun by the 10th day of foetal life (61, 62). Many older observations show that during late pregnancy there is an increase in maternal adrenal cortical function, and Schwartz, Shirky & Steck (63), who compared the weight, ascorbic acid content and capacity for compensatory hypertrophy of the adrenals of pregnant and pseudopregnant rats, found evidence of a lower ACTH output in pseudopregnancy than during pregnancy. The clear experiments of Smith (64) demonstrate that in the pregnant monkey there is a source of ACTH other than the maternal pituitary, for the adrenal glands of hypophysectomized pregnant animals were well maintained. Apart from the maternal pituitary, therefore, two sites of origin of ACTH may be postulated: the foetal pituitary or the placenta.

The question of placental transfer of maternal ACTH to the foetus is not yet closely answered. Since the adrenals of decapitated foetuses fail to develop normally it would appear that maternal ACTH does not cross the placental barrier (61). Holland (65) in a brief report on the effects of hypoxia in pregnant rats found that the foetal adrenal glands were reduced in size at a simulated altitude of 18,000 feet. He concluded that the raised concentration of adrenal steroids in the maternal blood was effective in inhibiting ACTH secretion by the foetal pituitary, but that maternal ACTH did not affect the foetal adrenals directly. Opposing evidence, indicating that maternal ACTH does cross the placental barrier, at least if present in greatly increased amounts, has also been produced. Knobil & Briggs (66) recorded a highly significant increase in foetal adrenal weight after adrenalectomy of the mother, but the adrenal weight gain of the foetus was prevented by previous hypophysectomy of the mother. This latter procedure alone did not reduce the foetal adrenal weight. The passage of adrenal corticoids across the placenta has been studied by Gunberg (67) who injected hydrocortisone into pregnant rats and found reduced adrenal weights in the foetuses. That this observation may be explained by placental transfer of hydrocortisone with reduction in foetal pituitary secretion of ACTH is made probable by the finding of a raised concentration of hydrocortisone in blood from the umbilical cord following intravenous administration of this hormone to the human mother just prior to Caesarian section (68).

Although the foetal pituitary is able to secrete ACTH it has been reported that the pituitary-adrenal axis of the newborn rat is unable to respond to certain stresses such as the injection of epinephrine or exposure to cold (69). Since the adrenal cortex of the newborn animal is able to respond to injection of ACTH (70, 71, 72), the lack of a stress response cannot be due to insensitivity of the adrenal gland. Further, the finding of Rinfret & Hane (72), that the anterior pituitary of 4 to 7 day old rats contains appreciable amounts of ACTH, indicates the potentiality of the pituitary to respond

to stresses. The lack of sensitivity of the pituitary-adrenal axis of the newborn animal may be the result of lack of development of some neural (hypothalamic) mechanism, a consideration which has recently been discussed (73). It is of interest that the pituitary gland of the adult rabbit isolated from the hypothalamus (74) secretes ACTH in response to certain types of noxious stimuli (injection of large doses of epinephrine, laparotomy) but not to others (restraint, cold exposure). If certain types of stress require intact hypothalamo-hypophysial connections the pattern of stress responses in the newborn animal might be compared with that of the pituitary stalk-sectioned adult. At eight days of age the young rat responds to injection of adrenaline and laparotomy, but not to cold exposure (69, 75).

Control of Adrenal Cortical Activity

Response to emotional and surgical stress.—The fact that emotional stress activates the adrenal medulla and cortex affords strong evidence that the central nervous system can affect, either directly or indirectly, the activity of these glands. The studies of von Euler & Lundberg (76) have shown that an increased epinephrine secretion occurs during flight of both pilots and passengers. The data of Murphy & Cleghorn (77) indicates adrenocortical activation on the part of pilots flying jet planes, thus confirming the older observations of Pincus & Hoagland (78). Additional reports on the effect of various emotional states upon the activity of the adrenal cortex in the human have appeared (79 to 86). It seems that a marked eosinopenia is seen more frequently than a change in 17-hydroxycorticosteroids in the blood, though this latter was observed by Franksson & Gemzell (85) and by Bliss *et al.* (83). Hoagland *et al.* (81) observed more marked adrenocortical responses to emotional stress in older, rather than younger, men; however the observations of Tyler *et al.* (87) suggest that changes in the volume of distribution of the adrenal cortical secretion might in part explain these results. The effect of emotional stress (changes in light, noise, proximity of cats) on the histology of the pituitary gland and adrenal cortex of rats has been studied (88). An increase in pituitary size and number of basophils, with hypertrophy of the adrenal cortex was noted. The stress of captivity has been reported to produce a striking increase in the adrenal size of wild mice (89). The effect of emotional and other stresses on the blood eosinophils of the horse has been investigated (90).

The endocrine response of the human to surgical trauma has been discussed (91). Hume, Nelson & Miller (92) studied the plasma and urinary 17-hydroxycorticosteroids in 26 severely burned patients from the 4th to the 50th post-burn day. These patients showed increased adrenal cortical activity for as long as 16 to 17 days, indicating that a burn represents a prolonged stimulus to the hypothalamico-pituitary-adrenocortical mechanism. The adrenocortical response to major surgery was followed by Birke, Franksson & Plantin (93) who measured the output of 17-ketosteroids. Although the total excretion of 17-ketosteroids rose by only 45 per cent the postoperative

output of dehydroepiandrosterone showed a rise of 210 per cent. These workers found that the raised values of dehydroepiandrosterone generally provided a good indication of the increased adrenal activity in acute stress. This finding is supported by Paaby (94) who observed that only 67 per cent of patients showed an increased excretion of 17-ketosteroids although 96 per cent show a rise in the urinary dehydroisoandrosterone. Steenberg, Lennihan & Moore (95) found the rise in free serum 17-hydroxycorticoids to be early, steep, and massive, and found that the serum rise in 17-hydroxycorticoids following surgery was greater than that produced by maximal doses of ACTH given over similar periods of time. In explanation of this finding they suggest that trauma alters the metabolism or conjugation of 17-hydroxycorticoids since ACTH given in an early postoperative period produces a higher blood level of corticoids than when given in the normal or resting state. Bernhard *et al.* (96) investigated the effect of surgical trauma during operations under conditions of hypothermia and found that the 17-hydroxycorticoids in the arterial plasma of ten dogs and in the venous plasma of two patients did not change under these conditions. They observed a postoperative rise of 17-hydroxycorticoids which was less than would be expected after a comparable operation performed at normal temperature. Hypothermia itself did not produce a stress response. Nelson, Egdahl & Hume (97) report that cold exposure (−10°C. for 1 to 33 hr.) did not result in an increase in the rate of secretion of 17-hydroxycorticosteroids as estimated in the adrenal vein blood of conscious dogs. There was a rise however following warming after cold exposure. At lower environmental temperatures (−46° to −50°C., and −75° to −79°C.) Egdahl & Richards (98) found that conscious dogs responded with a marked increase in the concentration of 17-hydroxycorticosteroid in the adrenal vein blood. It is of interest that the response started soon after the onset of cold exposure and lasted for one to three hr., after which the hormone level dropped to the previous control value even though cold exposure was continued. That this was not owing to a failure of adrenal sensitivity was shown by administration of ACTH. As pointed out, it is important to note that healthy dogs show no fall in body temperature after exposure to −47°C. for 28 hr. or −79°C. for 5 hr. At low body temperatures the sensitivity of the adrenal cortex to ACTH may be depressed as suggested by the findings of Egdahl, Nelson & Hume (99a, 99b) and Georges & Cahn (100). Brodish & Long (101) used a cross-circulation technique to study the ACTH response of the rat to various stresses including surgical trauma and adrenalectomy. They report that the high rate of ACTH secretion which follows the application of a severe stress can be maintained for approximately two hours, after which the blood ACTH concentration gradually diminishes, disappears in six hours, and then slowly rises again. The disappearance of blood ACTH at six hours after the stress cannot be the result of an increased blood level of cortical hormones (since it occurs after bilateral adrenalectomy) and is not the result of pituitary exhaustion since a second stress applied at this time results in a marked rise in blood ACTH concentration.

Activity of the "isolated" pituitary gland.—In order to see clearly the extent of hypothalamic control over the anterior pituitary, the function of the "isolated" gland has been studied. The pituitary may be isolated from the hypothalamus by one of four methods: by permanent pituitary stalk-section, by lesions which destroy the infundibular region of the hypothalamus, by transplanting the pituitary to a remote site in the body and by culturing the gland *in vitro*. Since the possibility has been raised that pituitary stalk-section results in signs of glandular deficiency as a consequence of pituitary atrophy, several papers have dealt with the microanatomy of the pituitary after the stalk has been cut. Pituitary stalk-section in the ferret was found by Donovan & Harris (102) to result in atrophy of the neural lobe to 39 to 45 per cent of its normal volume, and of the anterior lobe to 80 to 95 per cent. In the rabbit Gaupp & Spatz (40) found degeneration of the isolated posterior lobe and some atrophy, but no necrosis, of the anterior lobe. Also in the rabbit Campbell & Harris (103) found that section of the stalk resulted in a neural lobe of 26 per cent of its normal volume and a *pars distalis* of 68 to 83 per cent. Russell (104) gives an account of the postmortem findings on two human patients submitted to surgical stalk-section. The anterior lobe was found to be extensively necrotic in both though, surprisingly, the posterior lobe was said to be normal. However, a wide-spread pathological condition around the pituitary region was present in both cases. When the above results are compared with those reported by Ganong, Frederickson & Hume (105) and Ganong & Hume (106) in the dog, i.e., that gonadal activity is only depressed by removing 75 per cent or more of anterior pituitary tissue, that thyroidal activity is depressed after removal of 80 per cent and adrenocortical function persists unless the hypophysectomy is complete, it would seem that loss of anterior pituitary function following stalk-section is not a result of ischaemic atrophy of the gland. It is more likely that this loss of pituitary activity results from loss of hypothalamic stimulation rather than reduction in the amount of the gland.

The effect of division of the pituitary stalk on adrenal size has been studied. In the ferret stalk-section followed by regeneration of the portal vessels was associated with adrenal glands of normal size, but after stalk-section with permanent interruption of the portal vessels the adrenal glands were significantly smaller (102). In the rabbit stalk-section likewise resulted in adrenal atrophy, though not to the extent seen in the hypophysectomized control (74). However in this species no difference was found in adrenal size between the animals with or without portal vessel regeneration across the site of section. In this latter study Fortier, Harris & McDonald also investigated the response of the various stalk-sectioned animals to the stresses of an injection of a large dose of epinephrine, laparotomy, cold exposure and restraint. All the stalk-sectioned animals retained a marked lymphopenic response to epinephrine and laparotomy and a marked fall in ascorbic acid following unilateral adrenalectomy. The lymphopenic response to cold and restraint recurred in those animals in which portal vessel regeneration was

observed in the final histological study, but was insignificant in the group assessed to have minimal vascular regeneration. These results therefore support the view originally proposed by Fortier (107) that stresses may be divided into at least two groups, neural or systemic, according to whether they activate ACTH release solely by mediation of the nervous system or also act on the pituitary through the general systemic circulation.

The results observed following lesions of the median eminence are in general agreement with those discussed above. Keller *et al.* (108) found, in dogs, that removal of the pituitary stalk and ventral hypothalamus did not prevent an eosinopenia following the "systemic" stress of laparotomy. They did not observe any adrenal atrophy following ventral hypothalamectomy. Two points should be considered in regard to this work. Firstly, Swingle *et al.* (109) find that adrenalectomy in the dog does not abolish an eosinopenic response to stress, and have produced evidence that under these conditions the eosinopenia results from histamine liberation (110). And secondly the adrenal weights of hypophysectomized dogs may not differ very markedly from those of normal animals (108). Complete separation of the pituitary from the hypothalamus by median eminence lesions was found by Laqueur *et al.* (111) to result in the loss of the eosinopenia to stress and reduced amounts of 17-hydroxycorticosteroids in the adrenal vein blood of cats. A differentiation between the effects of a systemic stimulus (histamine injection) and a neural stimulus (sound) was made by Mialhe-Voloss (112, 113) who reports that the systemic stimulus results in a decreased ACTH content of the anterior lobe of the pituitary and the neural stimulus a decreased content in the posterior lobe.

Pituitary transplantation to the anterior chamber of the eye has been found to result in a marked adrenal atrophy in male rats [Martini & de Poli (114)]. This atrophy appears less when calculated on a body weight basis, but the figures for the weights of the adrenals expressed in absolute figures are approximately 48 mg. for normal rats; 11 mg. for hypophysectomized rats; and 20 mg. for hypophysectomized-transplanted rats. These figures are in good agreement with those published previously [Harris & Jacobsohn (115); Fortier (116)]. Pituitary tissue cultured in roller tubes *in vitro*, although maintaining excellent growth and differentiation, failed to secrete ACTH unless hypothalamic tissue was added to the culture medium [Guillemin & Rosenberg (117)].

In summary then, there is evidence that the anterior pituitary gland, "isolated" from the influence of the hypothalamus, continues to secrete ACTH at a slow rate, and that this rate of release is no longer affected by nervous reflexes but may be increased by stresses which involve tissue trauma or metabolic disturbance.

Hypothalamic lesions and stimulation.—Hypothalamic lesions which do not disrupt the anatomical connection of the hypothalamus and hypophysis may, nevertheless, still disturb the normal secretion of ACTH. There is however lack of agreement regarding the site of the effective lesion. Fulford &

McCann (118) found that anterior hypothalamic lesions prevented compensatory adrenal hypertrophy, whilst lesions in the anterior and middle median eminence block the eosinopenia resulting from stress [Ganong, Frederickson & Hume (105)]. Measurement of the concentration of ACTH in systemic blood and of 17-hydroxycorticosteroid in adrenal vein blood by Hume & Nelson (119) revealed an absence of or marked diminution in the blood level of these hormones in association with lesions in the anterior part of the median eminence. There was no uniform correlation between these results and the occurrence of diabetes insipidus in the dogs. The adrenal hypertrophy evoked by amphenone [2:3-bis(*p*-aminophenyl)-2-methyl-1-propanone] administration was observed by Greer & Erwin (120) to be blocked by median eminence lesions in rats, though lesions in the posterior hypothalamus were without effect. On the other hand Endröczi & Mess (121) found that only posterior hypothalamic lesions in rats prevented the adrenal ascorbic acid depletion following the stress of unilateral adrenalectomy, and blocked the compensatory hypertrophy normally following unilateral adrenal removal. Slusher & Roberts (122) also found that lesions in the posterior hypothalamus just anterior to the mammillary body blocked the ascorbic acid depletion resulting from laparotomy, though a puzzling finding in this study is that polyuria was noted in the presence of intact hypothalamo-hypophysial tracts.

The effect of hypothalamic stimulation on ACTH release has received little attention in the past year. Katsuki *et al.* (123) stimulated the hypothalamus in cats and measured the adrenocorticoid concentration in adrenal vein blood and the sudanophil substance in the adrenal cortex. They recorded adrenal cortical activation after stimulating regions in the posterior hypothalamus [which is in agreement with the previous work of de Groot & Harris (124) and Porter (125, 126)]. In general accord with these results are those of Nakayama (127) who found electrical activation of regions in the posterior hypothalamus following intravenous injection of 20 μg. epinephrine or intraperitoneal injection of 1 mg. histamine. With larger doses of epinephrine similar effects were seen in the anterior hypothalamus.

Pharmacological blockade of the stress response.—During the last year more decisive results have been obtained with pharmacological blocking agents. Munson & Briggs (12, 128) have demonstrated that a single injection of morphine, in rats anaesthetized with sodium pentobarbital, will block the effect of such stresses as injection of histamine, epinephrine or vasopressin, laparotomy or unilateral adrenalectomy. Morphine alone exerts an initial excitatory effect on the nervous system and evokes discharge of ACTH (129). However rats pretreated with morphine for four days fail to show this excitatory effect and in this case morphine alone was shown to be sufficient to block the stress response (12) although neither morphine nor sodium pentobarbital affected the adrenal response to injection of ACTH. Ohler & Sevy (130) have confirmed the blockade of ACTH release by morphine following unilateral adrenalectomy, sham adrenalectomy and epinephrine injection. They found

that administration of adrenal cortical extract resulted in a partial blockade or that Dibenzyline [N-(2-chloroethyl)-N-(2-phenoxy isopropyl)-benzylamine] was ineffective.

Since it is likely that morphine acts, in the above respect, on the central nervous system rather than on pituitary cells directly, the above results as well as those of Hume (131), McCann (132) and Porter (125, 126) on hypothalamic lesions would imply that the effect of all stressful stimuli on ACTH release is mediated via the central nervous system. This is contrary to the deductions drawn from studies involving pituitary transplants [Cheng *et al.* (133), Fortier (116) and McDermott *et al.* (134)], and pituitary stalk-section [Fortier, Harris & McDonald (74)], which indicate a differentiation between "neural stresses" and "systemic stresses."

Since morphine blocks the action of endogenous epinephrine in exciting ACTH discharge, the conclusion has been drawn (12, 130) that endogenous epinephrine plays no primary role in ACTH secretion. Also, the morphine blockade of the effects of unilateral adrenalectomy has been interpreted by Munson & Briggs (12) as refuting the hypothesis that stressful stimuli increase the rate of ACTH secretion by causing a reduction in the concentration of blood corticoids.

A partial blockade of ACTH secretion by chlorpromazine (135 to 138) and by reserpine (139) has been found, though this is not supported by other studies (140 to 143). The hope that chlorpromazine-treated rats might replace hypophysectomized rats in the Sayer's test has not been fulfilled.

Studies of the blockading power and other activities of the halogenated corticosteroids give promise that these compounds will be of clinical importance (144 to 148).

Humoral transmitter in the hypophysial portal vessels.—The view that the hypophysial portal vessels regulate ACTH discharge from the adenohypophysis by transmitting a humoral substance from nerve endings in the median eminence to the cells of the *pars distalis* has received attention and indirect support from the results of several studies. Porter & Jones (149) have collected blood from the empty sella turcica of dogs, which they call portal vessel blood, and studied its ACTH-releasing potency by injection into rats pretreated with hydrocortisone (these rats failed to show adrenal ascorbic acid depletion following unilateral adrenalectomy). Such portal vessel blood was found to cause ascorbic acid depletion in hydrocortisone-inhibited rats, but not in hypophysectomized rats. Carotid blood did not cause ascorbic acid depletion in either the hydrocortisone-treated, or hypophysectomized, animals. Portal vessel plasma has been fractionated by Porter & Rumsfeld (150) and their results indicate that the substance responsible for pituitary activation is either a large protein molecule or is bound to a large protein molecule, and is probably not identical with vasopressin. Schapiro, Marmorston & Sobel (151) have studied the same problem by injecting blood from the head of a hypophysectomized rat into a rat with a lesion of the tuber cinereum or posterior hypothalamus. The recipient ani-

mals failed to respond to stress, but developed an eosinopenia if the hypophysectomized donor had been submitted to electric shock stress. This is taken to indicate the release of some substance into brain blood under stressful conditions which has the power to cause ACTH release from the pituitary.

Several reports of studies using *in vitro* preparations of the pituitary have appeared. Guillemin and his coworkers (117, 152, 153, 154) have used anterior pituitary tissue culture in roller tubes. Such cultures did not release ACTH into the fluid medium after the 8th day of incubation unless explants of the hypothalamus or median eminence were added to the culture. Addition of brain cortex, liver or spleen was without effect. Data were produced which show that histamine, acetylcholine, epinephrine, norepinephrine, serotonin, oxytocin, and vasopressin (known to be present in the hypothalamus) were not the compounds responsible for the effect of hypothalamic tissue (117). Commercial Pitressin also increased the ACTH release from pituitary cultures but since purified arginine-vasopressin had no effect the conclusion was drawn that the activity of the commercial Pitressin resulted from a contaminant (153). Results obtained after fractionation of hypothalamic and crude posterior pituitary extracts supported this view (154). The findings of similar studies by Saffran and his group in Montreal (155, 156, 157) are in general agreement. These workers used incubated pituitary and adrenal tissue with a chemical method for measuring adrenal cortical activity in the incubation medium. A corticotrophin-releasing factor was found in posterior pituitary extracts and in vasopressin prepared by the method of Stehle & Fraser. However the corticotrophin-releasing factor was found to be distinct from vasopressin and oxytocin, and its activity was found to be enhanced by norepinephrine. The active substance has now been isolated by paper chromatography.

A possible relationship of the neurohypophysis to ACTH release has been discussed by workers studying the neurosecretory material of the hypothalamus and posterior pituitary gland. Since the neurosecretory material is depleted under conditions which also evoke ACTH discharge, and is related in some way to posterior pituitary hormones, several workers have suggested (158 to 161) that this product of the hypothalamo-hypophysial tract is liberated into the portal vessels and plays the part of a humoral transmitter to the anterior pituitary. Allied with these observations are those drawing attention to the possibility of a direct relationship between antidiuretic hormone (ADH) and ACTH secretion by the *pars distalis*. McCann & Brobeck (162) reported that large doses of vasopressin caused increased adrenal cortical activity, and found a relationship between the site of hypothalamic lesions which produce diabetes insipidus and those which block ACTH discharge in response to stress. Subsequently Fulford & McCann (118) reported that the compensatory hypertrophy of the adrenal cortex which normally follows unilateral adrenalectomy was suppressed by hypothalamic lesions producing diabetes insipidus. Sayers & Burks (163) measured the ACTH activity of the blood of anaesthetized, adrenalectomized rats. Thirty minutes after the be-

ginning of ether anaesthesia this activity declined but could be brought back to its previous high figure by the injection of 5 units Pitressin, but not by injection of 10 units Pitocin or 10 μg. epinephrine. They suggest that a neurohumoral mechanism concerned with ACTH release is exhausted after 30 minutes of ether anaesthesia and that ADH (or some other factor in commercial Pitressin) can substitute for this neurohumor. Sayers (164) further reports that the blood ACTH concentration of the adrenalectomized rat after 30 minutes' ether anaesthesia is also increased by extracts of the rat neurohypophysis and by du Vigneaud's purified vasopressin, but not by extracts of spleen, muscle, or liver. He states that it remains to be proven that the action of ADH is directly on the adenohypophysis since Pitressin is equally effective whether given intravenously or into the internal carotid artery. Martini and his colleagues (114, 165, 166) have found that ADH and oxytocic hormone cause adrenal enlargement and an increased sudanophilic zone when injected into normal, but not hypophysectomized, rats. Inactivation of the hormones with thioglycollate caused loss of the ACTH releasing effect. Studies on hypophysectomized rats with intraocular pituitary transplants showed that administration of posterior pituitary hormones by intraperitoneal injection, or local injection in the grafted eye, caused an eosinopenia and a reduction in adrenal ascorbic acid. Since subconjunctival injection into the nongrafted eye had no effect this evidence indicates a direct action of the hormone on anterior pituitary tissue. Experiments by McDonald & Weise (167) and Shibusawa *et al.* (168) on the human have shown that administration of Pitressin is more effective in evoking adrenocortical activity than is administration of Pitocin.

The evidence that neurosecretory material or a posterior pituitary hormone is the humoral transmitter regulating ACTH release is equivocal. The observations of Guillemin and Saffran and their coworkers, the fact that Pitressin is not active in the morphine-treated rat [Munson & Briggs (12)], and the results of older studies discussed by Harris (169), would argue against this view. More work on this interesting speculation is needed.

Regulation of aldosterone secretion.—The results of current work indicate that the secretion of aldosterone is less under pituitary control than is the secretion of glucocorticoids. Rauschkolb, Farrell & Koletsky (170) examined the steroid content of adrenal vein blood of hypophysectomized and sham operated dogs. They found that the rate of secretion of aldosterone in the hypophysectomized animals was about 66 per cent that of the control dogs, whilst the rate of secretion of 17-hydroxycorticosterone, corticosterone, and 11-desoxy-17-hydroxycorticosterone had fallen to about 10 per cent. Previous studies by the same workers (171) had shown that administration of ACTH to hypophysectomized dogs had little effect on aldosterone secretion. Farrell, Banks & Koletsky (172) further investigated the inhibition of adrenal activity produced by administration of cortisone or 17-hydroxycorticosterone over a period of five weeks. Little evidence was obtained that the feed-back mechanism controlling ACTH secretion affected the adrenal output of aldo-

sterone or the histology of the zona glomerulosa of the adrenal. This agrees with the results of Simmons, Harvey & Hoshiko (173). Factors regulating the secretion by the isolated calf adrenal have been studied by Rosenfeld *et al.* (174). They found that addition of growth hormone or ACTH to the perfusing medium did not exert a definite effect on aldosterone secretion. However, a substantial Na/K imbalance in the medium induced a significantly augmented output of aldosterone-like materia[1]. This work confirms, in part, the older findings of Vogt (175) that the activity of the perfused adrenal gland of the dog may be increased by increasing the K/Na ratio of the perfusing fluid. A new clinical entity of primary aldosteronism has been described (176).

Pituitary-Adrenal-Thyroid Interrelationships

The adrenal cortex and stress in relationship to thyroid activity.—In the *Annual Reviews of Physiology*, Albert (177) and Barker (178) briefly discuss the relationship of the adrenal cortical steroids to thyroid function. More latterly evidence has accumulated that administration of ACTH or adrenal corticoids inhibits thyroid activity. Since Ingbar (179) has shown that cortisone produces an increase in the renal clearance of iodide, it is evident that measures of the rate of thyroidal uptake of I^{131} alone do not give a good index of thyroid activity under conditions of an increased blood concentration of adrenal corticoids. Studies in which the rate of release of thyroidal radioactivity was used to indicate thyroid function (180 to 184) are less influenced by changes in kidney function. Using this method it has been found that administration of ACTH or cortisone to the rabbit [Myant (183), Brown-Grant, Harris & Reichlin (185)] and to the rat [Brown-Grant (186)] resulted in a sudden and marked inhibition of the release of radioactive hormone from the thyroid gland. Brown-Grant (187) further showed that corticosterone and hydrocortisone have a similar effect on normal rabbits and rats, but that ACTH has no action in adrenalectomized rats. The mechanism by which adrenal corticoids inhibit thyroid activity is not entirely clear. It has been suggested that the steroids do not affect the pituitary secretion of TSH, since several workers (188, 189) have found that cortisone and ACTH do not depress the action of goitrogenic drugs. However this finding does not exclude the possibility that in the normal animal ACTH and cortisone affect thyroid function by depressing pituitary secretion. Indeed this seems the most likely explanation at the moment since cortisone was found not to affect the basal level of the thyroid/plasma iodide concentration ratios in hypophysectomized rats, nor the elevated level found in similar rats treated with TSH (179), and did not affect the action of exogenous TSH in liberating thyroid hormone in hypophysectomized rabbits (185).

Noxious or stressful stimuli have been found by most workers to inhibit thyroid activity. A reduction in the rate of I^{131} uptake by the thyroid gland of rats has been found to follow injection of typhoid vaccine, trauma, fasting, heat, cold (190), injection of formalin (191), injection of formalin, cordotomy

(192), anoxia, starvation, vitamin deficiency, nephrectomy (193), tourniquet shock (194), and exposure to low atmospheric pressure or high altitudes (195).

But again, measurement of the I^{131} uptake alone may not give a valid index of thyroid activity since stress, acting perhaps through the adrenal cortex, leads to an increased renal clearance of iodide [Bogoroch & Timiras (192)]. However studies using the rate of release of thyroidal radio-iodine have shown that emotional or painful stimuli, surgical trauma and injection of irritating solutions exert a prompt and marked inhibitory effect on the thyroid gland of normal and adrenalectomized rabbits [Brown-Grant, Harris & Reichlin (196)] and rats (187). The inhibitory influence of such stimuli is apparent within a few hours and may completely prevent the release of thyroid hormone for periods of 48 hours. Since the effect was seen after bilateral stellate ganglionectomy and after bilateral adrenalectomy it was suggested that the most likely mechanism involves a reduction in the secretion of TSH.

The relationship between ACTH and TSH secretion.—In view of the fact that stress uniformly excites the adrenal cortex and inhibits the thyroid gland it has been suggested that a reciprocal relationship between the secretion of ACTH and TSH might obtain at the pituitary level [Harris (197)]. If the rate of secretion of TSH is reduced by administration of exogenous thyroxine, adrenal hypertrophy occurs. It is known that under certain circumstances the secretion of ACTH and TSH may be simultaneously reduced as illustrated by the effects of administration of cortisone. But it is less certain that the secretion rate of both hormones may be simultaneously increased. The increased production of ACTH following noxious stimuli is accompanied by thyroidal inhibition (see above), and the increased production of TSH following thyroidectomy, myxoedema or administration of goitrogens is accompanied by reduced adrenal activity (198) and adrenal atrophy, although the adrenal gland retains its sensitivity to ACTH [Zarrow & Zarrow (199)]. The possible exceptions to this generalization would seem to follow exposure to cold or administration of amphenone. Recent work indicates that thyroid activity is increased in rabbits (184) and rats (200) by exposure to moderate degrees of cold (environmental temperature reduced from 27°-29°C. to 6.5°-15°C.) but that exposure to severe degrees of cold (0° to 2°C.) might result in thyroidal inhibition. Since 5°C. is the highest temperature at which consistent evidence of adrenocortical stimulation occurs in most strains of rats (201), it is possible that acute exposure to severe degrees of cold may act as a nonspecific stress to reduce the rate of secretion of TSH concurrently with an increased discharge of ACTH. The present information regarding the action of amphenone on the thyroid and adrenal cortex seems to be most easily explained on the grounds that TSH and ACTH secretion are simultaneously increased. However the mechanism of action of this drug on the adrenal is not entirely clear (202 to 206). According to Greer & Erwin (120) the thyroid and adrenal effects of amphenone can be differentiated at a hypothalamic level.

The hypothalamus and thyroid activity.—The thyroid gland still retains a residuum of activity after hypophysectomy. The uptake of I^{131} and the output of radioactive hormone by the thyroid (180, 184, 207) still continues though at a greatly reduced level. Similar observations have recently been made in the human (208, 209). The slight activity of the thyroid in the hypophysectomized animal is not affected by administration of exogenous thyroxine (210, 211) and simultaneous administration of thyroxine does not affect the action of exogenous TSH on the thyroid under these circumstances (211, 212). It would thus seem that there is no feed-back action of the thyroid hormone on the thyroid gland itself.

The effect of interrupting the anatomical connections between the hypothalamus and pituitary gland on the level of thyroid activity, on the feed-back mechanism of thyroid hormone and on the stress-induced inhibition of thyroid function has been examined in recent studies. Levels of thyroid activity intermediate between those of the normal and the hypophysectomized animal have been reported by Brown-Grant, Harris & Reichlin [see (196)] to follow pituitary stalk-section in rabbits, by Greer, Scow & Grobstein (213) after transplantation of the pituitary gland to the anterior chamber of the eye in mice, and by von Euler & Holmgren (214) after pituitary transplantation to the eye in rabbits. It would seem that intact connections between the hypothalamus and pituitary gland are necessary to maintain a normal secretion of TSH. Data regarding a hypothalamic or pituitary site of action of the feed-back of thyroid hormone are not conclusive. von Euler & Holmgren (212) found that injection of thyroxine into the pituitary gland inhibited the release of thyroidal I^{131}, though injection into the *tuber cinereum* was without effect. Further evidence in favour of a pituitary site of action is that administration of thyroxine still inhibits thyroid activity after pituitary stalk section (211) and after pituitary transplantation (210, 214). However Scow & Greer (210) did not see any marked change in thyroid weight after propylthiouracil feeding in mice with transplanted pituitaries. In keeping with this latter finding are the observations of Greer (215) and Bogdanove & Halmi (216) that hypothalamic lesions may block the goitrogenic action of thiouracil, which would indicate that the increased TSH secretion normally following a decrease of circulating thyroid hormone requires an intact hypothalamus. The effect of different types of stress stimuli on thyroid activity has been investigated by Brown-Grant, Harris & Reichlin [see (196)] after pituitary stalk section, and by von Euler & Holmgren (214) after pituitary transplantation. It was found that emotional stress (produced by restraint), prolonged anaesthesia and exposure to cold no longer affect thyroid function but that the surgical trauma of laparotomy still inhibits the thyroid gland. These findings support the thesis of Fortier (107) that stress stimuli of a purely neural or emotional type act on the anterior pituitary solely through the hypothalamus and pituitary stalk, but that noxious stimuli involving tissue trauma or gross metabolic disturbance may affect anterior pituitary function through changes in composition of the general systemic blood.

The effect of lesions restricted to particular localized sites in the hypo-

thalamus on the thyroid gland has been studied for many years. The old observations of Cahane & Cahane (217) are of interest in the light of recent findings. These workers studied the effect of various infundibular lesions on thyroid histology, and postulated the presence of two centres, one situated between the optic chiasma and pituitary stalk which excites the secretion of TSH and the other in the tubero-mammillary region which inhibits the secretion of this hormone. With the advent of radioactive iodine more precise measurements of thyroid activity in the presence of hypothalamic lesions have been made. It is of interest that several groups of workers have found lesions above and anterior to the median eminence of the tuber cinereum depress thyroid function. Greer (215, 218) first reported that bilateral lesions between the suprachiasmatic and caudal ventromedian nuclei result in thyroid atrophy, a loss of the goitrogenic response to thiouracil but no simultaneous interference with the thyroid/serum iodide concentration ratio. Bogdanove & Halmi (216) confirmed these findings and suggested the normal thyroid/serum iodide concentration ratio might be explained by the potentiation by propylthiouracil of the action of the residual TSH secretion. Ganong, Frederickson & Hume (105) have found that lesions placed in or just above the anterior border of the median eminence in dogs may depress the uptake of I^{131} by the thyroid to levels seen in hypophysectomized animals, and can result in histological signs of thyroid atrophy. It may be pointed out that in the above studies there is agreement that lesions in different parts of the hypothalamus may differentially affect the secretion of gonadotrophic hormone, ACTH and TSH [see Bogdanove, Spirtos & Halmi (219)]. Further data relating thyroid function to the anterior hypothalamus have been reported by Martini (220) who found that administration of propylthiouracil results in hypertrophy of the cells in the anterior hypothalamus and in the neurohypophysis.

The effect of electrical stimulation of the central nervous system on TSH secretion has recently received attention. Guinea-pigs subjected to diffuse electric shocks through the cranium showed an increase in the blood TSH within half an hour of the stimulus (221). Reference to previous work on the effects of electroshock may be found in this paper. More localized stimulation of the hypothalamus was found by Colfer (222) to result in histological signs of increased thyroid activity, provided the stimulus was applied for at least four one hr. periods in each of two days. No optimum site in the hypothalamus could be located but control stimulation applied to the thalamus or corpus callosum gave negative results. In a recent study, Harris & Woods (223) have investigated the effect of prolonged periods (usually 48 hr.) of electrical stimulation of different regions in the hypothalamus on the thyroid activity of rabbits. Intact unanaesthetized and unrestrained animals were stimulated by the remote control technique, and thyroid activity was assessed over the two to three weeks experimental period by means of the I^{131} release method. It was found that electrical stimulation in the region of the tuber cinereum rarely resulted in thyroid activation but more frequently in thyroid inhibition. In contrast to these results however were those seen in

many of the same animals after adrenalectomy and maintenance on constant daily doses of cortisone. Similar periods of stimulation then resulted in consistent and marked activation of the thyroid which was confirmed by measurement of the changes in the concentration of plasma protein bound I^{131}. Under these conditions hypothalamic stimulation was observed to maintain an increased level of thyroid activity even in the presence of a resultant rise in the concentration of thyroid hormone in the blood. It was suggested that the difference in the thyroid response before and after adrenalectomy was most probably a result of a sudden rise in the blood level of adrenal cortical hormone that occurs in the intact animal when the tuber cinereum is stimulated. As discussed above, adrenal corticoids appear to exert an inhibitory action on TSH secretion. In the adrenalectomized animal on constant cortisone therapy similar stimulation would fail to increase the blood corticoid level so that an increased secretion of TSH can occur.

Stress, adrenal cortex and Graves' disease.—Two factors which have been emphasized as of importance in the aetiology of Graves' disease are emotional stress and hypofunction of the adrenal cortex.

Several recent reports have summarized the extensive literature and added new information regarding the type of psychological trauma most commonly found to precede the onset of thyrotoxicosis. Ham, Alexander & Carmichael (224), Lidz & Whitehorn (225), Lidz (226, 227), Mandelbrote & Wittkower (228) and Kleinschmidt, Waxenberg & Cuker (229) have all emphasized the neurotic tendencies of such patients. Lidz & Whitehorn (225) conclude that Graves' disease frequently occurs in individuals who are highly dependent on interpersonal relationships for their security, and that disruption or threat of disruption of such relationship is apt to precipitate the disease. It is thus possible that psychic trauma leads in some way to increased discharge of TSH which in turn results in thyrotoxicosis.

Recent reports deal with the blood concentration of TSH in cases of hyperthyroidism (230, 231). Querido & Lameyer (230) have calculated the rise in concentration of TSH in the blood that would follow a dose of TSH sufficient to cause an increase in I^{131} uptake in the human thyroid. They believe that an increased thyroid activity may result from changes in the blood level of TSH that are too small to be detected by present assay methods. Negative findings regarding an increase in blood TSH in Graves' disease would therefore seem to lose much of their significance. More pertinent are the observations that some patients have a high concentration of TSH in the blood, and that this may be coexistent with a raised level of plasma protein-bound iodine (230, 231). A failure in the feed-back mechanism of the thyroid hormone is indicated and would imply the presence of an extrathyroidal abnormality.

The possibility that Graves' disease is associated with adrenal underactivity was pointed out by Marine & Baumann (232) and Marine (233). The clinical data on this aspect is suggestive though not clear cut, and may be summarized as follows:

(a) It has been said that occurrence of Graves' disease is high in patients already suffering from Addison's disease (234). Albert (177) feels this is an erroneous claim.

(b) The excretion of 17-ketosteroids (235, 236, 237) and of formaldehydogenic steroids (238) appears to be reduced in Graves' disease, although the excretion of reducing steroids may be normal or slightly increased (236, 239). Levin & Daughaday (240) found the excretion of 17-keto- and 17-hydroxysteroids to be within the normal range in thyrotoxicosis. The surprising feature of all these data is that the excretion rate of adrenal steroids is not greatly increased, since raising the blood concentration of thyroid hormone by administration of exogenous thyroxine results in increased adrenal activity and adrenal hypertrophy (241, 242), an increased excretion of 17-hydroxysteroids in the guinea-pig (240) and of 17-ketosteroids in man (237). The mental and physical condition of patients with Graves' disease would also seem to afford a strong stimulus to adrenal cortical hyperactivity. Levin & Daughaday (240) comment: "An inverse relationship between TSH and ACTH secretion by the pituitary is suggested to explain the discrepancy between the increased adrenocortical activity in animals treated with thyroid and the normal or decreased activity in Graves' disease."

(c) There are some data which indicate that administration of ACTH is beneficial in early cases of Graves' disease (243).

(d) A reduction in width of the adrenal cortex has been reported in postmortem examination of patients with Graves' disease (244) though this has not been a uniform finding according to the older literature. However the well-known autopsy findings of a large thymus and lymphoid hyperplasia, together with a tendency to lymphocytosis during life, are suggestive of adrenal underactivity. Crooke & Russell (245) reported that the thyroid gland in cases of Addison's disease may be histologically similar to that of Graves' disease. This observation is not in accordance with those of Sloper (246) and Bloodworth *et al.* (247).

In view of the experimental findings, described above, that electrical stimulation of the hypothalamus in the adrenalectomized rabbit may result in increased thyroid activity, and the clinical evidence connecting emotional trauma and a state of relative adrenal deficiency with Graves' disease, it would be of interest to investigate in more detail the effect of administering sedatives and ACTH to early and previously untreated cases of Graves' disease. Such a simple procedure appears free from hazard and is therefore suggested in full awareness of the difficulties involved in transferring the results obtained on experimental animals to the human patient, and of the conflicting nature of some of the clinical evidence involved.

Hypothalamic Inhibition of the Adenohypophysis

The possibility that the hypothalamus may exert an inhibitory influence over the adenohypophysis has rarely been discussed, except in relationship to the *pars intermedia*, and with regard to cases of *pubertas praecox* associated

with hypothalamic tumours in young children (248, 249). A possible reason is that, until recently, an inhibitory effect on gonadal, thyroidal, or adrenocortical activity has been difficult to measure.

Recent observations on the relation of the hypothalamus to gonadotrophic secretion raise the general question of hypothalamic inhibition over anterior pituitary secretion. It has been observed (250, 251) that bilateral lesions placed in the anterior region of the hypothalamus of female ferrets may be followed by the development of oestrus in the winter months of the year; that is, at a time of the year when the normal animal would be anoestrous. The possibility that this is a result of some stimulating effect of the lesion is unlikely since prolonged electrical stimulation of this area of the hypothalamus in other animals did not result in oestrus. In attempting to explain these results the possibility that the lesion has abolished some inhibitory, with consequent release of some excitatory, mechanism has to be considered. In this sense these results may have a different significance from those in which a state of constant oestrus is produced in rats or guinea pigs by lesions in the same area of the brain (252, 253), for these latter results may be attributable to damage to some neural mechanism involved in stimulating the release of luteinizing hormone.

It would be of much interest to investigate the possibility of hypothalamic inhibition over the secretion of ACTH and TSH, using the recent methods for assaying the blood concentration of ACTH and adrenal corticoids and radioactive iodine. It may be speculated that some form of reciprocal inhibition underlies many of the observations regarding an inverse relationship between the secretion of ACTH and TSH.

LITERATURE CITED

1. Pincus, G., and Thimann, K. V., *The Hormones*. Vol. III. (Academic Press, Inc., New York, N. Y., 1012 pp., 1955)
2. Noble, R. L., *The Hormones*. Vol. III, 685–819. (Pincus, G. and Thimann, K. V. Eds., Academic Press, Inc., New York, 1012 pp., 1955)
3. *Ciba Foundation Colloquia on Endocrinology*. Vol. VIII. The Human Adrenal Cortex. (Wolstenholme, G. E. W., and Cameron, M. P., Eds., J. and A. Churchill, Ltd., London, 665 pp., 1955)
4. *Hypothalamic-hypophysial interrelationships* (Fields, W. S., Guillemin, R., and Carton, C. A., Eds., Charles C Thomas, Springfield, Illinois, 156 pp., 1956)
5. Harris, G. W., *Neural Control of the Pituitary Gland* (Edward Arnold Ltd., London, 298 pp., 1955)
6. Bargmann, W. *Das Zwischenhirn-Hypophysensystem*. (Springer-Verlag, Berlin, Germany, 138 pp., 1954)
7. von Euler, U. S., *Fifth Annual Report on Stress*, 125–37. (Selye, H. and Heuser, G., Eds., MD Publications, Inc., New York, N. Y., 815 pp., 1956)
8. Gray, S. J., Ramsey, C. G., Villarreal, R., and Krakauer, L. J., *Fifth Annual Report on Stress*, 138–160. (Selye, H., and Heuser, G., Eds., MD Publications Inc., New York, N. Y., 815 pp., 1956),
9. Nelson, D. H., *Fifth Annual Report on Stress*. 169–184. (Selye, H., and Heuser, G., Eds., MD Publications, Inc., New York, N. Y., 815 pp., 1956)
10. Scharrer, E., *Fifth Annual Report on Stress*, 185–192. (Selye, H., and Heuser, G., Eds., MD Publications, Inc., New York, N. Y., 815 pp., 1956)
11. Ingle, D. J., *Fifth Annual Report on Stress*, 161–168. (Selye, H., and Heuser, G., Eds., MD Publications, Inc., New York, N. Y. 815 pp., 1956)
12. Munson, P. L., and Briggs, F. N., *Recent Prog. Hormone Research*, **11**, 83–107 (1955)
13. Cleghorn, R. A., *Psychosomat. Med.*, **17**, 367–76 (1955)
14. Cleghorn, R. A., *Can. J. Biochem. Physiol.*, **34**, 390–404 (1956)
15. Bush, I. E., *Schweiz. med. Wochschr.*, **85**, 645–48 (1955)
16. Knowlton, A. I., *Med. Clin. N. Amer.*, **39**, 811–29 (1955)
17. Laidlaw, J. C., Reddy, W. J., Jenkins, D., Haydar, N. A., Renold, A. E., and Thorn, G. W., *New Engl. J. Med.*, **253**, 747–53 (1955)
18. Sapeika, N., *Arch. Internal Med.*, **96**, 654–66 (1955)
19. Conn, J. W., *Arch. Internal Med.*, **97**, 135–44 (1956)
20. Gaunt, R., Renzi, A. A., and Chart, J. J., *J. Clin. Endocrinol.*, **15**, 621–46 (1955)
21. Prunty, F. T. G., McSwiney, R. R., and Mills, I. H., *Proc. Roy. Soc. Med.*, **48**, 629–32 (1955)
22. Simpson, S. A., and Tait, J. F., *Recent Progr. Hormone Research*, **11**, 183–210 (1955)
23. Furth, J., *Recent Progr. Hormone Research*, **11**, 221–49 (1955)
24. Gorbman, A., *Cancer Research*, **16**, 99–105 (1956)
25. Rawson, R. W., and Rall, J. E., *Recent Progr. Hormone Research*, **11**, 257–84 (1955)
26. van Dyke, H. B., Adamsons, K. Jr., and Engel, S. L., *Recent Progr. Hormone Research*, **11**, 1–35 (1955)
27. Metuzals, J., *Z. Zellforsch. u mikroskop. Anat.*, **43**, 319–34 (1955)
28. Palay, S. L. (Personal Communication)
29. Farquhar, M. G., and Rinehart, J. F. (Personal Communication)

30. Okada, M., Ban, T., and Kurotsu, T., *Med. J. Osaka Univ.*, **6**, 359–72 (1955)
31. Long, C. N. H., *Ann. Rev. Physiol.*, **18**, 409–32 (1956)
32. Worthington, W. C., *Bull. Johns Hopkins Hosp.*, **97**, 343–57 (1955)
33. Gregoretti, L., *Acta Neurovegetativa*, **12**, 25–40 (1955)
34. Engelhardt, F., *Acta Neurovegetativa*, **13**, 129–70 (1956)
35. Bölönyi, F., and Barta, I., *Acta morphol. Acad. Sci. Hung.*, **4**, 293–99 (1954)
36. Daniel, P. M., and Prichard, M. M. L., *Quart. J. Exptl. Physiol.*, **41**, 215–29 (1956)
37. Brettschneider, H., *Z. mikroscop.-anat. Forschung*, **62**, 30–39 (1956)
38. Gregoretti, L., *Acta Neurovegetativa*, **10**, 1–20 (1955)
39. Leonhardt, H., *Acta Neurovegetativa*, **12**, 41–52 (1955)
40. Gaupp, V., and Spatz, H., *Acta Neurovegetativa*, **12**, 285–328 (1955)
41. Hild, W., *Hypothalamic-hypophysial interrelationships*, 17–26. (Fields, W. S., Guillemin, R., and Carton, C. A., Eds., Charles C Thomas, Springfield, Ill., 156 pp., 1956)
42. Hanström, B., *Kgl. Fysiograf. Sällskap. i Lund Förh.*, **25**, 1–12 (1955)
43. Green, J. D., and van Breemen, V. L., *Am. J. Anat.*, **97**, 177–227 (1955)
44. Rothballer, A. B., *Acta Neurovegetativa*, **13**, 179–91 (1956)
45. Shibusawa, K., Inou, T., Osono, S., and Toshima, T., *Endocrinol. Japon.*, **1**, 89–98 (1954)
46. Imai, K., *Gunma Med. J.*, **3**, 281–96 (1954)
47. Purves, H. D., and Griesbach, W. E., *Endocrinology*, **49**, 244–64 (1951)
48. Purves, H. D., and Griesbach, W. E., *Endocrinology*, **56**, 374–86 (1955)
49. Jubb, K. V., and McEntee, K., *Cornell Vet.*, **45**, 593–641 (1955)
50. Siegel, J. H., *J. Morphol.*, **96**, 223–64 (1955)
51. Siperstein, E., Nichols, C. W., Griesbach, W. E., and Chaikoff, I. L., *Anat. Record*, **118**, 593–619 (1954)
52. Knigge, K. M., *Anat. Record*. **122**, 295–315 (1955)
53. Timmer, R. F., and Finerty, J. C., *Proc. Soc. Exptl. Biol. Med.*, **91**, 420–23 (1956)
54. Halmi, N. S., and Bogdanove, E. M., *Proc. Soc. Exptl. Biol. Med.*, **77**, 518–20 (1951)
55. Halmi, N. S., and Bogdanove, E. M., *Proc. Soc. Exptl. Biol. Med.*, **78**, 95–97 (1951)
56. Knigge, K. M., *Anat. Record*, **124**, 319 (1956)
57. Knigge, K. M., *Endocrinology*, **57**, 719–29 (1955)
58. Currie, A. R., and Symington, T., *Ciba Foundation Colloquia on Endocrinology*, **VIII**, 396–411 (1955)
59. Russfield, A. B., *J. Clin. Endocrinol.*, **15**, 1393–1408 (1955)
60. Del Conte, E., and Stux, M., *Acta Endocrinol.*, **20**, 246–56 (1955)
61. Wells, L. J., *Proc. Soc. Exptl. Biol. Med.*, **68**, 487–88 (1948)
62. Kitchell, R. L., and Wells, L. J., *Anat. Record*, **112**, 561–91 (1952)
63. Schwartz, N. B., Shirky, L. E., and Steck, I. E., *Endocrinology*, **57**, 114–19 (1955)
64. Smith, P. E., *Endocrinology*, **56**, 271–84 (1955)
65. Holland, R. C., *Anat. Record*, **124**, 306–07 (1956)
66. Knobil, E., and Briggs, F. N., *Endocrinology*, **57**, 147–52 (1955)
67. Gunberg, D. L., *Anat. Record.*, **124**, 399–300 (1956)
68. Migeon, C. J., Prystowsky, H., Grumbach, N. M., and Byron, M. C., *J. Clin. Invest.*, **35**, 488–93 (1956)

69. Jailer, J. W., *Endocrinology*, **46**, 420–25 (1950)
70. Jailer, J. W., Wong, S. H., and Engle, E. T., *J. Clin. Endocrinol.*, **11**, 186–92 (1951)
71. Bogin, M., Gottfried, S. P., and Levycky, N. V., *Am. J. Diseases Children*, **89**, 599–601 (1955)
72. Rinfret, A. P., and Hane, S., *Endocrinology*, **56**, 341–44 (1955)
73. Harris, G. W., *Biochemistry of the Developing Nervous System*, 431–42. (Waelsch H., Ed., Academic Press, Inc., New York, N. Y., 537 pp., 1955)
74. Fortier, C., Harris, G. W., and McDonald, I. R.—See Harris, G. W., *Ciba Foundation Colloquia on Endocrinology*, **VIII**, 531–50 (1955)
75. Rinfret, A. P., and Hane, S., *Endocrinology*, **57**, 497–99 (1955)
76. von Euler, U. S., and Lundberg, U., *J. Appl. Physiol.*, **6**, 551–55 (1954)
77. Murphy, C. W., and Cleghorn, R. A., *Can. J. Biochem. Physiol.*, **34**, 534–42 (1956)
78. Pincus, G., and Hoagland, H., *J. Aviation Med.*, **14**, 173–93 (1943)
79. Murphy, C. W., Kurlents, E., Cleghorn, R. A., and Hebb, D. O., *Can. J. Biochem. Physiol.*, **33**, 1062–63 (1955)
80. Kerr, A. C., *Quart. J. Exptl. Physiol.*, **41**, 18–24 (1956)
81. Hoagland, H., Bergen, J. R., Bloch, E., Elmadjian, F., and Gibree, N. R., *J. Appl. Physiol.*, **8**, 149–54 (1955)
82. Hill, S. R., *et al. Arch. Int. Med.*, **97**, 269–98 (1956)
83. Bliss, E. L., Migeon, C. J., Branch, C. H. H., and Samuels, L. T., *Psychosomat. Med.*, **18**, 56–76 (1956)
84. Hetzel, B. S., Schottstaedt, W. W., Grace, W. J., and Wolff, H. G., *J. Clin. Endocrinol.*, **15**, 1057–68 (1955)
85. Franksson, C., and Gemzell, C. A., *J. Clin. Endocrinol.*, **15**, 1069–72 (1955)
86. Crabbe, J., Riondel, A., and Mach, E., *Acta Endocrinol.*, **22**, 119–24 (1956)
87. Tyler, F. H., Eik-Nes, K., Sandberg, A. A., Florentin, A. A., and Samuels, L. T., *J. Am. Geriat. Soc.*, **3**, 79–84 (1955)
88. Näätänen, E. K., and Jänkälä, E. O., *Ann. Med. Exptl. et Biol. Fenniae (Helsinki)*, **32**, 410–18 (1954)
89. Dixon, W. C., *Anat. Record*, **124**, 281 (1956)
90. Alexander, F., and Ash, R. W., *J. Physiol. (London)*, **130**, 703–10 (1955)
91. Various authors. *Proc. Roy. Soc. Med.*, **48**, 817–22 (1955)
92. Hume, D. M., Nelson, D. H., and Miller, D. W., *Ann. Surg.*, **143**, 316–29 (1956)
93. Birke, C., Franksson, C., and Plantin, L.-O., *Acta Endocrinol.*, **18**, 201–09 (1955)
94. Paaby, H., *Acta Endocrinol.*, **21**, 337–42 (1956)
95. Steenberg, R. W., Lennihan, R., and Moore, F. D., *Ann. Surg.*, **143**, 180–209 (1956)
96. Bernhard, W. F., McMurray, J. D., Ganong, W. F., and Lennihan, R., *Ann. Surg.*, **143**, 210–15 (1956)
97. Nelson, D. H., Egdahl, R. H., and Hume, D. M., *Endocrinology*, **58**, 309–14 (1956)
98. Egdahl, R. H., and Richards, J. B., *Am. J. Physiol.*, **185**, 239–42 (1956)
99(a) Egdahl, R. H., Nelson, D. H., and Hume, D. M., *Science*, **121**, 506–07 (1955)
(b) *Surg, Gynecol. Obstet.*, **101**, 715–720 (1955)
100. Georges, G., and Cahn, J., *Compt. rend. soc. biol.*, **149**, 1775–78 (1955)
101. Brodish, A., and Long, C. N. H., *J. Clin. Endocrinol.*, **15**, 841 (1955)

102. Donovan, B. T., and Harris, G. W., *J. Physiol.* (*London*), **131,** 102–14 (1956)
103. Campbell, H. J., and Harris, G. W. (Unpublished data)
104. Russell, D. S., *Lancet*, **I,** 466–68 (1956)
105. Ganong, W. F., Frederickson, D. S., and Hume, D. M., *Endocrinology*, **57,** 355–62 (1955)
106. Ganong, W. F., and Hume, D. M., *J. Clin. Endocrinol.*, **15,** 843 (1955)
107. Fortier, C., *Endocrinology*, **49,** 782–88 (1951)
108. Keller, A. D., Lynch, J. R., Batsel, H. L., Witt, D. M., and Galvin, R. D., *Am. J. Physiol.*, **179,** 5–14 (1954)
109. Swingle, W. W., Eisler, M., Ben, M., Maxwell, R., Baker, C., and LeBrie, S. J. *Am. J. Physiol.*, **178,** 341–45 (1954)
110. Swingle, W. W., Eisler, M., Baker, C., LeBrie, S. J., and Brannick, L. J. *Am. J. Physiol.*, **182,** 256–62 (1955)
111. Laqueur, G. L., McCann, S. M., Schreiner, L. H., Rosemberg, E., Rioch, D. McK., and Anderson, E., *Endocrinology*, **57,** 44–54 (1955)
112. Mialhe-Voloss, C., *Compt. rend. acad. sci.*, **241,** 105–107 (1955)
113. Mialhe-Voloss, C., *Ann. Endocrinol.*, **17,** 104–109 (1956)
114. Martini, L., and de Poli, A., *J. Endocrinol.*, **13,** 229–34 (1956)
115. Harris, G. W., and Jacobsohn, D., *Proc. Roy. Soc.* (*London*) [B], **139,** 263–76 (1952)
116. Fortier, C., *Ciba Foundation Colloquia on Endocrinology*, **IV,** 124–36 (1952)
117. Guillemin, R., and Rosenberg, B., *Endocrinology*, **57,** 599–607 (1955)
118. Fulford, B. D., and McCann, S. M., *Proc. Soc. Exptl. Biol. Med.*, **90,** 78–80 (1955)
119. Hume, D. M., and Nelson, D. H., *J. Clin. Endocrinol.*, **15,** 839–40 (1955)
120. Greer, M. A., and Erwin, H. L., *Endocrinology*, **58,** 665–670 (1956)
121. Endröczi, E., and Mess, B., *Endokrinologie*, **33,** 1–8 (1955)
122. Slusher, M. A., and Roberts, S., *Federation Proc.*, **15,** 173 (1956)
123. Katsuki, S., Ikemoto, T., Shimada, H., Hagiwara, F., and Kanai, J., *Endocrinol. Japon.*, **2,** 303–12 (1955)
124. de Groot, J., and Harris, G. W., *J. Physiol.* (*London*), **111,** 335–46 (1950)
125. Porter, R. W., *Am. J. Physiol.*, **172,** 515–19 (1953)
126. Porter, R. W., *Recent Progr. Hormone Research*, **10,** 1–18 (1954)
127. Nakayama, T., *Japan. J. Physiol.*, **5,** 311–16 (1955)
128. Briggs, F. N., and Munson, P. L., *Endocrinology*, **57,** 205–19 (1955)
129. George, R., and Way, E. L., *Brit. J. Pharmacol.*, **10,** 260–64 (1955)
130. Ohler, E. A., and Sevy, R. W., *Am. J. Physiol.*, **183,** 649 (1955)
131. Hume, D. M., *Ann. Surg.*, **138,** 548–557 (1953)
132. McCann, S. M., *Am. J. Physiol.*, **175,** 13–20 (1953)
133. Cheng, C. P., Sayers, G., Goodman, L. S., and Swinyard, C. A., *Am. J. Physiol.*, **159,** 426–32 (1949)
134. McDermott, W. V., Fry, E. G., Brobeck, J. R., and Long, C. N. H., *Proc. Soc. Exptl. Biol. Med.*, **73,** 609–10 (1950)
135. Olling, C. C. J., and de Wied, D., *Acta Endocrinol.*, **22,** 283–92 (1956)
136. Hamburger, C., *Acta Endocrinol.*, **20,** 383–90 (1955)
137. Cheymol, J., Leeuw, J. D., Henry, R., and Oger, J., *Ann. endocrinol.* (*Paris*), **15,** 857–62 (1954)
138. Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., Yamada, H., and Tomizawa, K., *Endocrinol. Japon.*, **2,** 189–94 (1955)
139. Rindani, T. H., *Arch. intern. pharmacodynamie*, **102,** 465–69 (1955)

140. Gaunt, R., Renzi, A. A., Antonchak, N., Miller, G. J., and Gilman, M., *Ann. N. Y. Acad. Sci.*, **59**, 22–35 (1954)
141. Cheng, D. W., *Anat. Record*, **124**, 272–273 (1956)
142. Egdahl, R. H., and Richards, J. B., *Am. J. Physiol.*, **185**, 235–38 (1956)
143. Egdahl, R. H., Richards, J. B., and Hume, D. M., *Science*, **123**, 418 (1956)
144. Kessler, W. B., Varney, R. F., and Borman, A., *J. Clin. Endocrinol.*, **15**, 849 (1955)
145. Kupperman, H. S., Blatt, M. H. G., and Wiesbader, H., *J. Clin. Endocrinol.*, **15**, 850–51 (1955)
146. Kupperman, H. S., Blatt, M. H. G., Vesell, M., Gagliani, J., Wiesbader, H., and Vosburg, L., *J. Clin. Endocrinol.*, **15**, 911–22 (1955)
147. Thorn, G. W., Renold, A. E., Morse, W. I., Goldfien, A., and Reddy, W. J., *Ann. Intern. Med.*, **43**, 979–1000 (1955)
148. Goldfien, A., Saint-Marc, J., Beigelman, P. M., and Ganong, W. F., *J. Clin. Endocrinol.*, **15**, 850 (1955)
149. Porter, J. C., and Jones, J. C., *Endocrinology*, **58**, 62–67 (1956)
150. Porter, J. C., and Rumsfeld, H. W., *Endocrinology*, **58**, 359–64 (1956)
151. Schapiro, S., Marmorston, J., and Sobel, H., *Proc. Soc. Exptl. Biol. Med.*, **91**, 382–86 (1956)
152. Guillemin, R., *Hypothalamic-hypophysial interrelationships*, 46–57. (Fields, W. S., Guillemin, R., and Carton, C. A., Eds., Charles C Thomas, Springfield, Illinois, 156 pp., 1956)
153. Guillemin, R., and Hearn, W. R., *Proc. Soc. Exptl. Biol. Med.*, **89**, 365–67 (1955)
154. Guillemin, R., Hearn, W. R., Cheek, W. R. and Housholder, D. E., *Federation Proc.*, **15**, 84 (1956)
155. Saffran, M., and Schally, A. V., *Can. J. Biochem. Physiol.*, **33**, 408–15 (1955)
156. Saffran, M., Schally, A. V., and Benfey, B. G., *J. Clin. Endocrinol.*, **15**, 840 (1955)
157. Saffran, M., Schally, A. V., and Benfey, B. G., *Endocrinology*, **57**, 439–44 (1955)
158. Rothballer, A. B., *Anat. Record*, **115**, 21–41 (1953)
159. Benoit, J., and Assenmacher, I., *Arch. Anat. micr.*, **42**, 334–86 (1953)
160. Palay, S. L., *Am. J. Anat.*, **93**, 107–27 (1953)
161. Scharrer, E., and Scharrer, B., *Recent Progr. Hormone Research*, **10**, 183–232 (1954)
162. McCann, S. M., and Brobeck, J. R., *Proc. Soc. Exptl. Biol. Med.*, **87**, 318–24 (1954)
163. Sayers, G., and Burks, R., *J. Clin. Endocrinol.*, **15**, 840–41 (1955)
164. Sayers, G., *Federation Proc.*, **15**, 162 (1956)
165. Martini, L., de Poli, A., and Curri, S., *Proc. Soc. Exptl. Biol. Med.*, **91**, 490–93 (1956)
166. Martini, L., and Morpurgo, C., *Nature*, **175**, 1127–28 (1955)
167. McDonald, R. K., and Weise, V. K., *Proc. Soc. Exptl. Biol. Med.*, **92**, 107–10 (1956)
168. Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., and Yoshimura, F., *Endocrinol. Japon.*, **2**, 47–56 (1955)
169. Harris, G. W., *Hypothalamic-hypophysial interrelationships*, 146–47 (Fields, W. S., Guillemin, R., and Carton, C. A., Eds., Charles C Thomas, Springfield, Illinois, 156 pp., 1956)

170. Rauschkolb, E. W., Farrell, G. L., and Koletsky, S., *Am. J. Physiol.*, **184,** 55–58 (1956)
171. Farrell, G. L., Rauschkolb, E. W., and Royce, P. C., *Am. J. Physiol.*, **182,** 269–72 (1955)
172. Farrell, G. L., Banks, R. C., and Koletsky, S., *Endocrinology*, **58,** 104–08 (1956)
173. Simmons, D. H., Harvey, R. B., and Hoshiko, T., *Am. J. Physiol.*, **181,** 379–89 (1955)
174. Rosenfeld, G., Rosemberg, E., Ungar, F., and Dorfman, R. I., *Endocrinology*, **58,** 255–61 (1956)
175. Vogt, M., *J. Physiol.* (*London*), **113,** 129–56 (1951)
176. Conn, J. W., and Lawrence, L. H., *Ann. Internal Med.*, **44,** 1–15 (1956)
177. Albert, A., *Ann. Rev. Physiol.*, **14,** 481–98 (1952)
178. Barker, S. B., *Ann. Rev. Physiol.*, **17,** 417–42 (1955)
179. Ingbar, S. H., *Endocrinology*, **53,** 171–81 (1953)
180. Wolff, J., *Endocrinology*, **48,** 284–97 (1951)
181. Albert, A., *Endocrinology*, **48,** 334–38 (1951)
182. Perry, W. F., *Endocrinology*, **48,** 643–50 (1951)
183. Myant, N. B., *J. Physiol.* (*London*), **120,** 288–97 (1953)
184. Brown-Grant, K., von Euler, C., Harris, G. W., and Reichlin, S., *J. Physiol.* (*London*), **126,** 1–28 (1954)
185. Brown-Grant, K., Harris, G. W., and Reichlin, S., *J. Physiol.* (*London*), **126,** 41–51 (1954)
186. Brown-Grant, K., *Endocrinology*, **56,** 607–09 (1955)
187. Brown-Grant, K., *J. Physiol.* (*London*), **131,** 58–69 (1956)
188. D'Angelo, S. A., Stevens, C. E., Paschkis, K. E., and Cantarow, A., *Proc. Soc. Exptl. Biol. Med.*, **83,** 181–84 (1953)
189. O'Neal, L. W., and Heinbecker, P., *Endocrinology*, **53,** 239–41 (1953)
190. Williams, R. H., Jaffe, H., and Kemp, C., *Am. J. Physiol.*, **159,** 291–97 (1949)
191. Paschkis, K. E., Cantarow, A., Eberhard, T., and Boyle, D., *Proc. Soc. Exptl. Biol. Med.*, **73,** 116–18 (1950)
192. Bogoroch, R., and Timiras, P., *Endocrinology*, **49,** 548–56 (1951)
193. van Middlesworth, L., and Berry, M. M., *Am. J. Physiol.*, **167,** 576–80 (1951)
194. Hamolsky, M. W., Gierlach, Z. S., and Jensen, H., *Am. J. Physiol.*, **164,** 35–43 (1951)
195. Verzár, F., Sailer, E., and Vidovic, V., *J. Endocrinol.*, **8,** 308–20 (1952)
196. Brown-Grant, K., Harris, G. W., and Reichlin, S., *J. Physiol.* (*London*), **126,** 29–40 (1954)
197. Harris, G. W., *Ciba Foundation Colloquia on Endocrinology*, **VIII,** 531–50 (1955)
198. Eik-Nes, K., and Brizzee, K. R., *Am. J. Physiol.*, **184,** 371–75 (1956)
199. Zarrow, M. X., and Zarrow, I. G., *Proc. Soc. Exptl. Biol. Med.*, **76,** 620–23 (1950)
200. Brown-Grant, K., *J. Physiol.* (*London*), **131,** 52–57 (1956)
201. Deane, H. W., and Lyman, C. P., *Endocrinology*, **55,** 300–15 (1954)
202. Hogness, J. R., Lee, N. D., and Williams, R. H., *Endocrinology*, **52,** 378–89 (1953)
203. Hertz, R., Tullner, W. W., Schricker, J. A., Dhyse, F. G., and Hallman, L. F., *Recent Progr. Hormone Research*, **11,** 119–41 (1955)
204. Hertz, R., Pittman, J. A., and Graff, M. M., *J. Clin. Endocrinol.*, **16,** 705–23 (1956)
205. Tullner, W. W., Graff, M. M., and Hertz, R., *Endocrinology*, **58,** 802–07 (1956)

206. Thorn, G. W., Renold, A. E., Goldfien, A., Nelson, D. H., Reddy, W. J., and Hertz, R., *New Engl. J. Med.*, **254,** 547–51 (1956)
207. Randall, R. V., Lorenz, N., and Albert, A., *Endocrinology*, **48,** 339–40 (1951)
208. Li, M. C., Rall, J. E., MacLean, J. P., Lipsett, M. B., Ray, B. S., and Pearson, O. H., *J. Clin. Endocrinol.*, **15,** 1228–38 (1955)
209. Pearson, O. H., Ray, B. S., Harrold, C. C., West, C. D., Li, M. C., MacLean, J. P., and Lipsett, M. B., *J. Am. Med. Assoc.*, **161,** 17–21 (1956)
210. Scow, R. O., and Greer, M. A., *Endocrinology*, **56,** 590–96 (1955)
211. Brown-Grant, K., Harris, G. W., and Reichlin, S. (Unpublished data)
212. von Euler, C., and Holmgren, B., *J. Physiol. (London)*, **131,** 125–36 (1956)
213. Greer, M. A., Scow, R. O., and Grobstein, C., *Proc. Soc. Exptl. Biol. Med.*, **82,** 28–30 (1953)
214. von Euler, C., and Holmgren, B., *J. Physiol. (London)*, **131,** 137–46 (1956)
215. Greer, M. A., *J. Clin. Endocrinol.*, **12,** 1259–68 (1952)
216. Bogdanove, E. M., and Halmi, N. S., *Endocrinology*, **53,** 274–92 (1953)
217. Cahane, M., and Cahane, T., *Acta Med. Scand.*, **94,** 320–27 (1938)
218. Greer, M. A., *Proc. Soc. Exptl. Biol. Med.*, **77,** 603–08 (1951)
219. Bogdanove, E. M., Spirtos, B. N., and Halmi, N. S., *Endocrinology*, **57,** 302–15 (1955)
220. Martini, L., *Arch. intern. pharmacodynamie*, **101,** 68–80 (1955)
221. Del Conte, E., Ravello, J. J., and Stux, M., *Acta Endocrinol.*, **18,** 8–14 (1955)
222. Colfer, H. F., *Trans. Am. Goiter Assoc.*, 376–78 (1949)
223. Harris, G. W., and Woods, J. W., *Nature*, **178,** 80–81 (1956)
224. Ham, G. C., Alexander, F., and Carmichael, H. T., *Research Publ. Assoc. Nervous Mental Diseases*, **29,** 451–57 (1950)
225. Lidz, T., and Whitehorn, J. C., *Research Publ. Assoc. Nervous Mental Diseases*, **29,** 445–50 (1950)
226. Lidz, T., *J. Mount Sinai Hosp.*, **20,** 27–40 (1953)
227. Lidz, T., *Psychosomat. Med.*, **17,** 420–27 (1955)
228. Mandelbrote, B. M., and Wittkower, E. D., *Psychosomat. Med.*, **17,** 109–23 (1955)
229. Kleinschmidt, H. J., Waxenberg, S. E., and Cuker, R., *J. Mount Sinai Hosp.*, **23,** 131–53 (1956)
230. Querido, A., and Lameyer, L. D. F., *Proc. Roy. Soc. Med.*, **49,** 209–12 (1956)
231. Gilliland, I. C., and Strudwick, J. I., *Brit. Med. J.*, **I,** 378–81 (1956)
232. Marine, D., and Baumann, E. J., *Am. J. Physiol.*, **57,** 135–52 (1921)
233. Marine, D., *Am. J. Sci.*, **180,** 767–72 (1930)
234. Fredrickson, D. S., *J. Clin. Endocrinol.*, **11,** 760 (1951)
235. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., *J. Clin. Endocrinol.*, **1,** 234–56 (1951)
236. Shadaksharappa, K., Calloway, N. O., Kyle, R. H., and Keeton, R. W., *J. Clin. Endocrinol.*, **11,** 1383–94 (1951)
237. Corvilain, J., *Brit. Med. J.*, **II,** 915–17 (1953)
238. Daughaday, W. M., Jaffe, H., and Williams, R. H., *J. Clin. Endocrinol.*, **8,** 244–56 (1948)
239. Talbot, N. B., Wood, M. S., Worcester, J., Christo, E., Campbell, A. M., and Zygmuntowicz, A. S., *J. Clin. Endocrinol.*, **11,** 1224–36 (1951)
240. Levin, M. E., and Daughaday, W. M., *J. Clin. Endocrinol.*, **15,** 1499–1511 (1955)

241. Wallach, D. P., and Reineke, E. P., *Endocrinology*, **45**, 75–81 (1949)
242. Timiras, P. S., and Woodbury, D. M., *J. Pharmacol. Exptl. Therap.*, **115**, 144–53 (1955)
243. Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W., *J. Clin. Endocrinol.*, **10**, 1375–1400 (1950)
244. LeCompte, P. M., *J. Clin. Endocrinol.*, **9**, 158–62 (1949)
245. Crooke, A. C., and Russell, D. S., *J. Pathol. Bact.*, **40**, 255–83 (1935)
246. Sloper, J. C., *J. Pathol. Bact.*, **66**, 53–61 (1953)
247. Bloodworth, J. M. B., Kirkendall, W. M., and Carr, T. L., *J. Clin. Endocrinol.*, **14**, 540–53 (1954)
248. Weinberger, L. M., and Grant, F. C., *Arch. Internal Med.*, **67**, 762–92 (1941)
249. Bauer, H. G., *J. Clin. Endocrinol.*, **14**, 13–31 (1954)
250. Donovan, B. T., and van der Werff ten Bosch, J. J., *J. Physiol. (London)*, **132**, 57P–58P (1956)
251. Donovan, B. T., and van der Werff ten Bosch, J. J., *Proc. III Intern. Congr. Animal Reproduction* [I], 75–77 (1956)
252. Dey, F. L., *Endocrinology*, **33**, 75–82 (1943)
253. Hillarp, N.-A., *Acta Endocrinol.*, **2**, 11–23 (1949)

REPRODUCTION[1,2]

By Charles H. Sawyer and B. Vaughn Critchlow

Department of Anatomy, School of Medicine, University of California and Veteran's Administration Hospital, Long Beach, California

The first half of the long-awaited Volume I of *Marshall's Physiology of Reproduction* has appeared (1). It deals in an encyclopedic manner and a phylogenetic approach with such subjects as breeding seasons, morphology of reproductive organs, and cyclic changes in the female. Marshall himself contributed to two of the six chapters, and he was joined in the dedicated task by Mathews, Brambell, Eckstein and Zuckerman; the last two authors sharing responsibility for well over half the volume. The literature coverage reaches beyond 1950, and remarkable progress is recorded for the period since the 1922 edition appeared.

The reports of several important symposia have also been published. "The Comparative Physiology of Reproduction" is a stimulating discussion of reproductive patterns and the effects of sex hormones and gonadotrophins in the various classes of vertebrates and in the fetus (2). The 1955 "Studies on fertility" contain several interesting basic and clinical contributions (3). The Second Macy Conference on Gestation goes into problems of psychology in pregnancy and lactation, delayed implantation and structural and functional studies on uteroplacental circulation (4). The 1954 Laurentian Conference considers the chemistry, physiology, metabolism, and control of pituitary hormones and problems of aging as reflected in the gonads (5). Reference will be made to some of these papers below.

Neuroendocrine Function, Hypophysis, Gonadotrophins

Neuroendocrinology may be said to have "come of age." Several comprehensive treatments of problems related to nervous control of the hypophysis have appeared, including Harris' authoritative monograph (6), Benoit & Assenmacher's beautifully detailed review of hypothalamo-gonadotrophic controls (7), a stimulating symposium on hypothalamichypophyseal interrelationships (8) and a briefer review (9).

Several investigations have attempted to demonstrate, by morphological methods or lesioning techniques, the areas of the brain which control gonadotrophic function. Lesions in the basal tuber or median eminence have induced ovarian atrophy in the cat [Laqueur *et al.* (10)] (11), the dog [Ganong

[1] The period surveyed included July, 1955 to June, 1956, but the May and June issues of some of the foreign journals were not available in time to be considered.

[2] The following abbreviations have been employed in this chapter: FSH (follicle stimulating hormone); LH (luteinizing hormone); ICSH (interstitial cell stimulating hormone); LTH (luteotrophin); HCG (human chorionic gonadotrophin); PMS (pregnant mare serum gonadotrophin); ACTH (corticotrophin); TSH (thyrotrophin).

et al. (12)] and the rabbit (13). In the rabbit a wide variety of rhinencephalic lesions failed to block copulation-induced ovulation (13). The role of the nervous system in establishing cyclic pituitary activity has been reemphasized for the rat (14). Blockade of the castration cell response and the absence of both gonadotrophs and gonadotrophin are associated with hypothalamic lesions which induce testicular atrophy in male rats [Bogdanove *et al.* (15)]. Hertl has reported nucleolar (16) and nuclear volume changes in the infundibular nucleus of the mouse hypothalamus (17) correlated with various phases of the female reproductive cycle. Transecting the hypophyseal stalk in laying hens has affected gonadal activity more severely than thyroid or adrenal function (18). Lesions around the pineal body in female rats have upset sex function presumably by damage to structures around the third ventricle (19). In a review of clinical cases of sexual precocity Jolly (20) has emphasized that pineal tumors are involved only indirectly as they affect the posterior hypothalamus. Another clinical condition brought on by hypothalamic tumors is amenorrhea (21).

Inasmuch as the neurohypophyseal hormone oxytocin affects uterine motility and milk ejection, neurosecretion studies (22, 23, 24) are pertinent. Malandra has demonstrated in the rat an increase in neurosecretion during the second half of pregnancy and a decrease during lactation (25). Croxatto and his colleagues (26, 27, 28) have assayed the oxytocic activity of the rat hypothalamus, and they report an increased concentration of the hormone in the tuber within a half hour after hypophysectomy. Hypothalamic production of oxytocin might explain the normal egg-laying capacity of neurohypophysectomized hens [Shirley & Nalbandov (29)]. The suggestion has been made repeatedly that vasopressin derived from neurosecretory processes and imported via the portal system (8, 30) stimulates the release of adenohypophyseal ACTH; however, such views have been sharply criticized (6). Saffran *et al.* (31) report an ACTH-stimulating factor distinct from oxytocin or vasopressin in posterior pituitary extracts, the activity of which is enhanced by arterenol. Adrenergic substances have also been shown to exert a stimulatory action on the metabolism of the posterior hypothalamus and the adenohypophysis directly [Roberts & Keller (32)]. Recent work has suggested that gonadotrophin [Shibusawa *et al.* (33)] and prolactin [Benson & Folley (34)] secretion may be triggered by oxytocin, and Jöchle proposed that intermedin might act as an activator of gonadotrophin release (35). Regardless of the nature of the transmitter substances, the neurohumoral-pituitary portal system hypothesis is widely accepted (6, 7). However, there are skeptics [Eckstein & Zuckerman (1), Gaupp & Spatz (36)], and the theory of direct innervation of anterior lobe gland cells still has a champion in Metuzals (37).

Pharmacological blockade of the release of pituitary ovulating hormone has been the subject of further studies. Hough *et al.* (38) have found that progesterone-advancement of ovulation in the cow is blocked by atropine,

confirming earlier findings in the rat (39). Barraclough *et al.* have shown that morphine (40) and chlorpromazine (41), both of which upset reproductive cycles in the human (42), block the release of ovulatory hormone in the rat if injected before 2 P.M. on the day of proestrus. These agents, like atropine, raise thresholds in the brainstem reticular formation, and the results suggest that afferent nerve pathways to the hypothalamus may include these multisynaptic, extralemniscal routes [Sawyer *et al.* (43)]. Blockade at this site rather than in the hypothalamus per se may also account for morphine's inhibitory action on the pituitary-adrenal axis [Munson & Briggs (44)]. Chlorpromazine is reported to block neurosecretion of oxytocin (45), yet it stimulates the release of prolactin [Sulman & Winnik (46)] (47). Chlorpromazine induces abortion in rats if given between the sixth and tenth days of pregnancy [Chambon (48)]. Pituitary gonadotrophins may act as "blocking agents" in the release of ovulating hormone in the hen if they are injected several hours prior to natural release [Fraps & Fevold (49), see also Fraps' illuminating discussion of these problems (2)].

Some insight has been gained into the mechanisms by which environmental factors affect gonadotrophic function. Donovan & Harris report perfect correlation between regeneration of portal vessels and light-induced estrus in the ferret (50). Cervical sympathectomy delays the estrus response to light, apparently by diminishing the amount of light impinging on the retina (51). The effects of light on vaginal changes in the rat have been interpreted in terms of light stimulating release of FSH (52). Exposure to low ambient temperatures under controlled lighting conditions lengthened the rat estrus cycle by prolonging the proestrus and estrus stages [Denison and Zarrow (53)]. Artificially-maintained low environmental temperature in summer advanced estrus some eight weeks in ewes (54). Incidence of "spontaneous" pseudopregnancy in mice is elevated by some social factor attendant upon grouping several previously solitary females together (55). Electric shock has upset the estrus cycle in rats (56) and the menstrual cycle in humans [Michael (57)].

Several interesting effects of hormones on behavior have appeared. The hormonal stimulus for spawning in Fundulus, formerly attributed to LH, has been traced to oxytocin, still another reproductive function of this neurohypophyseal product [Wilhelmi *et al.* (58)]. Nesting behavior in the hen is related to its pituitary prolactin content (59), and nest building by the mouse can be evoked by progesterone (60). Karli describes the maternal drive of the full-term pregnant rat towards an adult mouse (4, 61). The effects of androgen [Riss *et al.* (62)] and adrenal steroids (63, 64, 65) on sex behavior in male guinea pigs, rats and hamsters have been studied. Beach *et al.* (66) have described frontal lesions in the male cat which did not reduce sexual excitability, and Green and collaborators (67) have found that small lesions in the pyriform cortex lead to marked hypersexuality. On the other hand, small lesions in the anterior hypothalamus (cat) and mammillary

nuclei (rabbit) eliminate mating behavior in the female, even in the presence of exogenous estrogen (11).

Cowie & Folley (68) have admirably reviewed the physiology of gonadotrophins and prolactin, including a discussion of their cellular origin. A careful study of pituitary cell types correlated with various hormonal and seasonal conditions in the female bat has been made by Herlant (69). Knigge (70) suggests that argyrophilic cells in the rat hypophysis may be identical with gonadotrophs. An increase in disulfide and sulfhydryl groups in basophils following castration has been interpreted as reflecting an increased content of FSH or LH, or both [Ladman & Barrnett (71)]. Young male rats require twice as much estrogen as do females to inhibit the formation of castration cells [Hoogstra & de Jongh (72)].

In the monkey menstrual cycle Simpson *et al.* (73) have found pituitary FSH and ICSH content greatest between days 9 to 11, with the highest ICSH/FSH ratio (10 to 1) occurring around the time of ovulation (days 11 to 15). Female mule deer pituitaries have a seasonal peak in gonadotrophin content in the autumn around the time of mating; the level declines sharply after early pregnancy [Grieser & Browman (74)]. The high gonadotrophic activity repeatedly found in the pituitaries of young female rats has been shown by Hoogstra & Paesi (75) to be due to FSH only.

In a study of the effects of female sex steroids and HCG on rat pituitary cytology, the HCG-induced rise in chromophils actually precedes the estrogen effect (76). Everett (77) has demonstrated that in pituitary grafts which secrete growth hormone and LTH, release of LTH can be induced by an excess of estrogen; vaginal mucification occurs which reverts to cornification on removal of the transplant. Meyers and Clifton, in an interesting series of papers, have found that stilbestrol indirectly stimulates TSH secretion; elevates pituitary proteinase activity; and directly induces the secretion of prolactin, with a related increase in the mitotic activity of the prolactin-producing acidophils that eventually results in tumors (78, 79, 80, 81). Pituitary hypertrophy in response to estradiol or stilbestrol was partially counteracted if another estrogen, tri-phenyl-anisyl chloroethylene, was given simultaneously [Segal & Thompson (82)]. By itself the latter does not cause hypertrophy. P-hydroxy-propiophenone appears to inhibit growth hormone, LH, TSH; to stimulate ACTH and to leave FSH and prolactin unaffected (83).

Some of the functions and mechanisms of pituitary and urinary gonadotrophins have received attention. Histochemical changes in endocrine glands on treatment with FSH, LH or ACTH include marked alterations in alkaline phosphatase activity and the periodic acid-Schiff reaction (84). Gonadotrophins were more consistent than estrogen or progesterone in causing the immature rat vagina to open (85). Das & Nalbandov (86) have shown that there are qualitative differences between avian and mammalian pituitary gonadotrophins. HCG is ineffective in inducing ovulation in hypophysectomized rats unless given directly after operation (87); the failure appears to be

due at least in part to lack of adrenal steroids (88). In this connection, HCG was found to stimulate the uptake of radiophosphorus by the rat adrenal (89) but could not be demonstrated to stimulate estrogen production in the castrate mouse adrenal (90). There are reports that HCG may contain some FSH activity (91), and menopause urinary gonadotrophin, some LH activity (92). Improved methods of extracting (93) and assaying (94, 95) nonpregnancy urine gonadotrophin have been presented. Several other papers on the separation of gonadotrophins (96, 97), the precision of bioassay (98, 99) and factors complicating assay procedures (100, 101) have appeared. Attention should be called to an extended critique on methods by Diczfalusy & Heinrichs (102).

Reproduction in the Female

Sex cycles.—Chapters 4 and 6 of *Marshall's Physiology* (1) by Eckstein & Zuckerman are excellent reviews of estrus cycles and the female reproductive system, respectively. A 12- to 14-day estrus cycle in laboratory cats has been described by Scott & Lloyd-Jacob (3). In the rat cycle, vaginal epithelial nucleic acids (103) and blood levels of thyroid and thyrotrophic hormones (104) reached their peak during estrus; however, Brown-Grant found no correlation between stages of the cycle and the rate of I^{131} uptake and release from the thyroid (105). Rats become sterile normally at 24 to 28 months, or earlier under irradiation (106), and hamsters between 11 to 19 months (107). Mandl & Zuckerman (108) were unable to confirm Parkes' earlier report that mice, sterilized by x-irradiation, run estrus cycles. Sterilized mice and rats both showed irregular vaginal changes followed by persistent cornification and later persistent anestrus. Bastian & Zarrow (109) have presented a new hypothesis for the asynchronous cycle of the hen.

Anovulatory menstrual cycles in women are unpredictable and may occur with widely varying degrees of ovarian follicular activity [Allende (110)]. Gilbert & Gilman (111) find that estrogen-withdrawal bleeding in the baboon requires adrenal and thyroid participation. Bartelmez challenges the "myth of endometrial arteriovenous anastomoses" with a review of the evidence for arterial constriction as the cause for ischemia and endometrial injury; coiling of the arteries is not essential for menstruation (112). Cyclic changes occur in endometrial glycogen (113), urinary 17-hydroxycorticoids (114) and in phenolic steroids (115).

Ovary.—Brambell's review (1) contains basic data on the development of ova, follicles, corpora lutea, and interstitial cells. Several new studies have implicated the interstitital cells as the probable source of estrogen (116, 117, 118). Interstitial tissue develops from transformed granulosa cells of atretic follicles in the hamster ovary [Knigge & Leathem (119)].

The immature rat ovary contains about 1900 primordial oocytes (120). New oocytes appear to be formed all through the reproductive life of several species of mammals (121), but they were not observed to be produced in ovarian grafts (122). In the hypophysectomized rat solid medium-sized

follicles may be developed in direct response to estrogen [Payne & Hellbaum (123)]. In the cycling rat the temporal relationships between the onset of heat and the stages of maturation of the ovum have been determined by Odor (124). The process of ovulation as observed in the living rat is described by Blandau (125). The failure of ovulation in the mouse and related changes in the reproductive tract following a single injection of testosterone at five days of age have been discussed by Barraclough (126). Allende & Orias (127) have reviewed the brilliant experimental work of the Houssay laboratory on ovulation in the toad.

Corpora lutea of pregnant and pseudopregnant rats have been studied with the electron microscope (128) and by histochemical methods [Dawson & Verlardo (129)]. The corpora of anestrous ewes, ovulated with PMS, have been kept functional for 20 to 30 days with daily prolactin treatment [Moore & Nalbandov (130)]. Changes in the human *corpus luteum* relative to the menstrual cycle have been recorded [Corner (131)].

In clinical cases of virilism Westman (132) and Scott (133) observed cystic ovaries covered by a thickened tunic; artificially thickening the ovarian tunic in monkeys did not prevent ovulation. Unusual activation of fetal ovaries was correlated with maternal toxemia (134).

Parkes (135) has been able to maintain subcutaneous interstrain ovarian homografts in the rat for over a year; they were characterized by follicular cysts correlated with persistent vaginal cornification. In similar transplants, especially in her autograft series, Deanesly observed normal cyclic ovulation, with pseudopregnancy following mating (136). Kullander (137, 138) reports that rat ovarian tissue autografted into the spleen produced enough progesterone to support deciduoma formation (137, 138), and Desclin (139) presents evidence that they also produce androgen. In the hamster Takewaki found such transplants underwent atresia unless estrogen or androgen was supplied (140). Embryonic rat ovaries, transplanted with an embryonic testis under the kidney capsule of a castrate adult rat, were inhibited in development by the testis [Macintyre (141)].

Female reproductive tract.—Several "form and function" studies on the oviduct, uterus, and vagina have employed histochemical methods. The occurrence, distribution and hormonal dependence or both, of the following substrates, inclusion bodies or enzymes have been investigated: glycogen (142, 143, 144), lipide (145), pigment (146, 147), alkaline phosphatase (148, 149), carbonic anhydrase (150), amylophosphorylase (151), and lipase (152). The nuclear volume of rat endometrial cells is much increased by estrogen (153). The electron microscope has been used to study the epithelia of the rabbit oviduct (154) and the human vagina (155). Melton (156) has recorded electrical activity in the estrous rat uterus in the form of low amplitude slow waves or high fast spikes of 1 to 2 mv. and a propagation speed of about 4 cm./sec.

Estrogens.—Diczfalusy *et al.* (157) report that treatment with polyestradiol phosphate, a long-acting estrogen, is followed by excretion of natural estro-

gens in ovariectomized women; the prolonged effectiveness is related to its high blood level (158). Castrate female rats with ovaries implanted into their spleens seem to inactivate extrinsic estrogen faster than ordinary castrates (159). The excretion of estrogen into bile and its presence in meconium have been demonstrated (160, 161). Hepatomatous or cirrhotic livers lose their capacity to combine estrogens to protein [Szego (162)]. It is suggested that estrogens are transported in part via lymphatics (163) and stored in visceral fat (164).

The effects of estrogens on the uterus are many and varied. They greatly increase the following phenomena: the permeability to sodium and serum albumin [Kalman (165)], the incorporation of formate and glycine (166), the synthesis of actotropomysin (167), and the deposition of collagen (168). Estrogen-induced weight gain is augmented by cholinergic drugs (169). Aldolase activity (170) and the lactic-dehydrogenase-DPNH oxidase system [Bever, Velardo & Hisaw (171)] are stimulated. Mitosis is activated probably as a result of the stimulation of the glucokinase system (172). Confirming Csapo's *in vitro* work, Schofield (173) has found *in vivo* that uterine contractions are stronger and longer-lasting under estrogen than under progesterone domination.

Velardo & Sturgis (174) have shown that the uterine weight increase in response to estradiol 17β is counteracted by 16 epi-estriol, a very weak estrogen (175). Other estrogen-antagonizing agents include the adrenal glucocorticoids and ACTH (176, 177), in part confirming earlier findings of Roberts & Szego. Huggins & Jenson (178) have reported depression of estrone-induced uterine growth by "impeded" estrogens such as estriol or by progesterone derivatives; progesterone also depresses the growth stimulating activity of high doses of estriol but enhances growth induced by low doses (179). Relatively low dosages of estrogen and progesterone act synergistically on the growth of the chick oviduct [Breneman (180)], but higher levels of progesterone or Reichstein's Substance S depresses the estrogen effect [Tullner & Hertz (181)]. Stilbestrol stimulation of chick oviduct growth requires vitamin B_{12} (182). Folic acid reinforces the pre-puberal rat uterine response to estrogen [Penhos (183)]. Growth but not survival of rabit vaginal grafts is stimulated by estrogen [Krohn (184)].

Progesterone.—A chromatographic progesterone-assay method is described (185) and used to demonstrate the hormone "stored" in fatty tissue [Kaufmann & Zander (186)]. About 1 per cent of the progesterone in human serum is in the free form, while the rest is bound to albumin [Westphal (187)]. Trolle calculates that during the luteal phase of the normal menstrual cycle 260 to 440 mg. progesterone are produced (188). Strong progestational effects on the endometrium have been reported for desoxycorticosterone-hexahydrobenzoate (189), halogenated glucocorticoids [Hertz & Tullner (190)] and 19-norethinyltestosterone (191). Davis & Wied (192) report a much prolonged activity from 17-alpha-hydroxyprogesterone, but Mardones *et al.* (193) find this agent much less potent than progesterone in

antifibromatogenic and antihysterotrophic activity. Several other progesterone derivatives have been tested for anti-luteinizing potency (194). Other progesterone data are reviewed below under "Pregnancy."

Relaxin.—Hall (195) has shown that prolonged treatment of the ovariectomized mouse with various combinations of estrogens and progesterone does not produce the pelvic changes which can be obtained with estrogen and relaxin; such changes can be evoked in either sex by estrogen and relaxin at three weeks of age [Crelin (196)]. Ganschow (197), using toxic doses of diethylstilbestrol, reported similar effects at this age without relaxin. The relaxin content of the blood serum of dairy cows reaches a high plateau level at the sixth month of pregnancy and drops to one-fifth this value within 24 hours after parturition (198). Clinically, relaxin has shown promising results in slowing labor, and there are indications that it may soften the cervix (199). Noall & Frieden (200) have stressed the need for a standard preparation in the assay of relaxin and have proposed a method for its standardization.

Fertility and fertilization.—The desperate need for agents and methods of controlling human population growth has been discussed (201). The Population Council program directed by W. O. Nelson is devoted to this end. Other investigations include those of Wiesner & Yudkin (202) who report promising results in mice with D-usnic acid and Podophyllotoxin. East (203) has studied the antifertility effects of a wide variety of plant preparations, some of which are estrogens. Genistein induces vaginal cornification in female mice and is very effective in sterilizing male mice (204). Lithosperm diminishes or abolishes the activity of gonadotrophic preparations *in vitro* [Loeser & Mikulicz (205)].

The stimulation (206), blockade (207) or agglutination of sperm (208) by cervical mucus are all factors in fertility. The progression of sperm in cervical mucus is greater than in Ringer's solution but is not correlated with the phases of the menstrual cycle nor with proven fertility (209). The importance of uterine contractions (210, 211, 212) and oxytocin (213) in transporting sperm to the upper end of the uterine horn and of intrinsic sperm motility in traversing the tube (211, 212) has been emphasized. In the rabbit Adams (214) found that although sperm reach the distal tip of the horn within 30 minutes of mating, 2 to 5 hours are needed before the number in the tube is sufficient to produce maximum fertilization. In the sow sperm resorption is rapid within the uterus but not in the tube (215).

Physical and chemical changes in the ovum at fertilization have been studied extensively in the sea urchin, and a symposium on the subject has been published (216). Austin has made a similar type of study on hamster eggs (217). Fertilization in this species *in vivo* occurs chiefly in the caudal third of the ampulla between 2 to 10 hours after ovulation (218). Labeling sperm with C^{14} has made it possible to differentiate male and female pronuclei at fertilization in the mouse [Edwards & Sirlin (219)]. Fertilized rabbit eggs show a sharp rise in respiratory metabolism at the stage of trans-

formation from morula to early blastocyst [Fridhandler *et al.* (220)]. Intra- and interspecies transplants of ova have been successful (221, 222, 223). Morphological characteristics of 34 human ova from the two-cell stage to the 17-day implanted specimen have been described by Hertig, Rock & Adams (224).

Pregnancy and placenta.—The finer morphology of the human placenta has been studied with the electron microscope [Wislocki & Dempsey (225)] and histochemical methods (226 to 229). Similar studies of the rat and rabbit placentae (230, 231) agree that they are hemochorial rather than hemoendothelial in structure. Uteroplacental and fetal circulations are described in papers by Boyd, Burwell, Reynolds and Ramsey in *Gestation* (4). Considerations of blood flow (232), including pharmacological aspects (233) and fetal circulation (234, 235, 236), and a translation of Spanner's important concept (237) which is discussed and challenged by Ramsey (238) are among the available papers dealing with placental circulation. Physiological studies have considered the placental transfer of the following substances: sugars (239, 240, 241), lipides (242), oxygen (243), calcium (244), fluorides (245), and antibodies (246, 247). On experimental grounds the placenta has been suggested as a site of production of melanophore hormone (248) and anti-inflammatory substances (249), of conversion of progesterone to 6-keto-progesterone (250) and of interconversion of estrone and estradiol (251).

The merits, problems and inadequacies of the Galli-Mainini male frog spermiation test for pregnancy have been debated (252, 253, 254, 255). Urinary histidine (256) and electromyographic changes in abdominal musculature (257, 258) have been suggested as pregnancy tests. Van Wagenen & Simpson found that in the pregnant monkey, only urine excreted between days 22 and 34 of pregnancy had a gonadotrophic action (259).

The important role of progesterone in implantation [Hafez & Pincus (260)] and maintenance of pregnancy [Csapo (261)] has been stressed. Castration abortions (262, 263) as well as estrogen-induced abortions (264, to 268) have been largely attributed to either an absolute or relative deficiency of progesterone. Mechanisms of spacing of ova in the uterus have been discussed (269, 270, 271). Implantation during lactation is delayed due to reduced secretion of gonadotrophin and estrogen (272) or progesterone (273). Canivenc & Mayer (273) have produced a type of superfetation during lactation in the rat by inducing early implantation in only one uterine horn by local treatment with progesterone. Delayed implantation in the rat resulting from severe burning is also prevented by progesterone administration or adrenalectomy (274, 275). Progesterone similarly blocks the abortive action of cortisone in the rat (276). Sulman (277) disagrees with Shelesnyak & Davies (278) as to the effectiveness of antihistaminics in terminating pregnancy. The fetuses of rats on a Lathyrus pea diet do not survive through late pregnancy unless exogenous estrogen is supplied (279, 280).

The Rapp-Richardson saliva test for prenatal sex determinations has been sharply criticized (281). At least five groups of investigators indepen-

dently proposed the analysis of sex chromatin of cells in the amniotic fluid as a method of sexing fetuses, but there is possible danger to the fetus in obtaining samples (282 to 286).

In toxemia of pregnancy changes in salivary sodium concentrations indicate increased production of an adrenal salt-regulating hormone (287). Pituitrin-induced changes in water metabolism in rabbits (288) and uterorenal reflex vasoconstriction [Franklin & Winstone (289)] are thought to be analogous to toxemic changes. The role of plasma proteins in normal and in toxemic pregnancies has been reviewed (290).

New measurements have been made of plasma progesterone (291), conjugated corticoids (292), oxytocinase (293), and fibrinogen (294) during pregnancy. Variations in palmar sweating (295) and changes in the urinary excretion of estrogens (296), gonadotrophin (297), aldosterone (298), and neutral steroids (299, 300) have also been studied in relation to pregnancy.

Mammary gland and lactation.—Recent studies on optimal estrogen/progesterone ratios for mammary gland growth in rabbits (301) and rats (302) reemphasize species differences in mammary physiology. A strain difference in mammary development after castration has been described for mice (303). Benson *et al.* (304) found normal mammary growth and milk yield in goats with estrogen and progesterone treatment with or without "triggering" doses of estrogen; estrogen alone induced histological abnormalities. Although the adrenals are essential in early lactation, only the *corpus luteum* is necessary in later stages (305). Glucocorticoids can cause duct growth and secretory activity (306). Thyroidectomy in rats is compatible with lactation (307). The effects of prolactin on the mammary gland have been observed in mice (308), rats (34), and rabbits (309).

Ringler & Nelson (310) found no change in succinoxidase activity and coenzyme A concentration in lactating guinea pig glands that had been hormonally stimulated; however, Tuba *et al.* (311) found significant increases in mitochondrial cytochrome oxidase and succinoxidase activity correlated with natural lactation in rats. The electron microscope has been used for the study of mammary cell structure and the process of milk secretion (312); slight changes in size and possibly in numbers of mitochondria associated with lactation have been described (313). On the other hand, Williams & Turner (314) feel that nucleoprotein, not mitochondria, is the target for prolactin. The metabolism of I^{131} by the mammary gland has been studied by Brown-Grant (105). Eayrs & Baddeley, in an important and interesting paper, describe some of the neural pathways by which suckling maintains lactation (315). Lyons *et al.* have reported on mammary growth and lactation in male rats, and Folley has discussed the effects of hormones on lactation at an international symposium on growth hormone (316).

Reproduction in the Male

Testis and male reproductive tract.—Clermont & Morgenthaler (317) have shown in a careful quantitative study that spermatogenesis may proceed to spermatid formation independently of hypophyseal hormones, but only a

very small number of cells reach this stage. The basophilia of developing germ layers of rat testis which is maximum at the end of the secondary spermatocyte stage is inversely related to arginine content (318). The importance of dietary protein for the maturation of the testis and spermatogenesis (319) and for the maintenance of normal testicular weight, protein, and glycogen levels (320) has been stressed. Methionine may be an essential amino acid for spermatogensis (321).

Several workers have studied induced testicular damage. Experimental cryptorchidism damaged spermatozoa, spermatids, and finally spermatocytes, a sequence suggesting nonspecific injury (322). The spermatogenic element most sensitive to irradiation has not yet been clearly defined, but Oakberg (323) and Bryan *et al.* (324) agree that the most sensitive period is between late interphase and early prophase. Cadmium produces severe testicular necrosis (325). Large doses of testosterone prevent damage to the testis from thiourea (326) and thyroxine (327). Estrogens may damage the testes directly [Bacon & Kirkman (328)]. Marshall and his colleagues, in studies related to cyclic changes in the testes of birds, have shown that hypophysectomy (329) or high doses of prolactin (330) induce degenerative changes in the testes which are very similar to those seen at the end of the breeding season.

Male infertility remains a problem. Clinical evidence for testicular secretion of estrogens supports the suggestion that some male infertility may be due to inhibition of FSH secretion (331). Although seminal fructose levels continue to be of little value for the diagnosis of infertility, the rate of utilization of fructose by sperm is correlated with the fertilization capacity of bull semen (332, 333). A difference in the chromatographic distribution of seminal amino acids in azoospermic and fertile men has been described (334). High serum inorganic phosphorus may indicate impaired gondal function (335). Interest in the obscure "rebound phenomenon" continues, and some success is claimed for treatment of infertile men with testosterone (336) and ethinyl estradiol (337).

Mann *et al.* have extended their studies of semen and have described the composition, the quantities, and the sequence of vesicular and ampullar contributions to the normal stallion ejaculate (338). The participation of fructose, ergothioneine, and citric acid of seminal plasma during the passage of sperm in the female reproductive tract has been studied (339).

Several papers report on the metabolism of the seminal vesicle. The roles and intracellular distributions of hexokinase and acid and alkaline phosphatases have been described (340); early findings regarding relationships to vesicular lipide metabolism, acid phosphatase concentration, and formation of fructose have been confirmed (341); some of the general metabolic characteristics of the gland have been investigated (342).

Androgens.—A monograph on androgens by Dorfman & Shipley (343) promises to be an invaluable aid for those interested in the many aspects of the "male hormones."

A rather rapid increase in seminal fructose indicates that scrotal insula-

tion in the ram causes an increase in androgen levels (344); however, some clinical evidence points to a subnormal endocrine activity in cryptorchid testes (345). Androgen has been isolated from human peripheral plasma (346); it is bound to the albumin fraction of the plasma proteins (347); and biologically-active androgens have been demonstrated in bile of testosterone-treated rats with intact livers (348).

Adreno-testicular relationships continue to attract considerable research attention. Cortisone has no specific effect on the spermatogenic function of the human testis (349), on the germinal and interstitial elements of the rabbit testis (350), or on the interstitial cells of the rat (351). Androgen production by the fetal zone of the adrenal has been studied in humans (352), and in hamsters (353). Benirschke *et al.* (354) suggest, after a study of anencephalics, that chorionic gonadotrophins and fetal pituitary LH are responsible sequentially for the maintenance of the fetal zone.

Kochakian *et al.* (355, 356) have continued their work on the effects of castration on muscle metabolism. The protein anabolic effects of methyl-androstenediol are dependent on the age of the animal, are seen only in certain muscles, and are associated with a reduction in the myofibrillar ATP-ase activity in the muscles stimulated [Korner & Young (357, 358, 359)]. Johnsen has described a method for the chromatographic separation of urinary androgen metabolites with which he was able to derive average values and normal ranges of urinary ketosteroids and which may be of clinical diagnostic value (360).[3]

[3] The authors gratefully acknowledge the help of Mrs. Pearl Ruttenberg, Mrs. Jessamine Hilliard, and Mrs. Irene Freyer in finding and checking references and typing the manuscript.

LITERATURE CITED

1. *Marshall's Physiology of Reproduction*, Vol. 1, Pt. 1 (Parkes, A. S. (Ed.), Longmans, Green and Co., London, England 688 pp., 1956)
2. *The comparative physiology of reproduction and the effects of sex hormones in vertebrates, Memoirs of the Society for Endocrinology No. 4* (Jones, I. C., and Eckstein, P., eds., Cambridge, University Press, Cambridge, England, 253 pp., 1955)
3. *Studies on Fertility, Proc. Soc. Study of Fertility*, Vol. 7 (Harrison, R. G. Ed., Blackwell Scientific Publications, Oxford, England, 156 pp., 1955)
4. *Transactions of the Second Conference on Gestation*, (Villee, C. .A (Ed.), Josiah Macy Jr. Foundation, New York, N. Y., 262 pp., 1956)
5. *Recent Progress in Hormone Research*, Vol. 11 (Academic Press, New York, N. Y., 518 pp., 1955)
6. Harris, G. W., *Neural Control of the Pituitary Gland* (Edward Arnold, London, England, 298 pp., 1955)
7. Benoit, J., and Assenmacher, I., *J. Physiol. (Paris)*, **47**, 427–567 (1955)
8. *Hypothalamic-Hypophysial Interrelationships* (Fields, W. S., Guillemin, R., and Carton, C. A., (Eds.), Charles C. Thomas, Springfield, Ill., 156 pp., 1956)
9. Cleghorn, R. A., *Psychomat. Med.*, **17**, 367–76 (1955)
10. Laqueur, G. L., McCann, S. M., Schreiner, L. H., Rosemberg, E., Rioch, D. M., and Anderson, E., *Endocrinology*, **57**, 44–54 (1955)
11. Sawyer, C. H., and Robison, B., *J. Clin. Endocrinol. Metabolism*, **16**, 914–15 (1956)
12. Ganong, W. F., Fredrickson, D. S., and Hume, D. M., *Endocrinology*, **57**, 355–62 (1955)
13. Sawyer, C. H., *Anat. Record*, **124**, 358 (1956)
14. Martinez, C., and Bittner, J. J., *Proc. Soc. Exptl. Biol. Med.*, **91**, 506–9 (1956)
15. Bogdanove, E. M., Spirtos, B. N., and Halmi, N. S., *Endocrinology*, **57**, 302–15 (1955)
16. Hertl, M., *Z. Zellforsch. u. Mikroskop. Anat.*, **41**, 207–20 (1955)
17. Hertl, M., *Z. Zellforsch. u. Mikroskop. Anat.*, **42**, 481–507 (1955)
18. Shirley, H. V., Jr., and Nalbandov, A. V., *Endocrinology*, **58**, 694–700 (1956)
19. Kurosawa, M., *Folia Psychiat. Neurol. Japon.*, **9**, 183–217 (1956)
20. Jolly, H., *Sexual Precocity* (Charles C Thomas, Springfield, Ill., 276 pp., 1955)
21. Kucsko, L., and Seitelberger, F., *Endokrinologie*, **32**, 136–46 (1955)
22. Green, J. D., and van Breemen, V. L., *Am. J. Anat.*, **97**, 177–227 (1955)
23. Adams, C. W. M., and Sloper, J. C., *J. Endocrinol.*, **13**, 221–28 (1956)
24. Mosier, H. D., *Endocrinology*, **57**, 661–69 (1955)
25. Malandra, B., *Z. Zellforsch. u. Mikroskop. Anat.*, **43**, 594–610 (1956)
26. Croxatto, H., and Zamorano, B., *Proc. Soc. Exptl. Biol. Med.*, **90**, 468–70 (1955)
27. Moreno, V. S., Croxatto, H., Aliste, N., and Ampuero, O., *Endocrinology*, **57**, 658–60 (1955)
28. Moreno, V. S., Zamorano, B., Croxatto, H., and Becerra, M., *Proc. Soc. Exptl. Biol. Med.*, **92**, 352–53 (1955)
29. Shirley, H. V., Jr., and Nalbandov, A. V., *Endocrinology*, **58**, 477–83 (1956)
30. Martini, L., and de Poli, A., *J. Endocrinol.*, **13**, 229–34 (1956)
31. Saffran, M., Schally, A. V., and Benfey, B. G., *Endocrinology*, **57**, 439–44 (1955)
32. Roberts, S., and Keller, M. R., *Endocrinology*, **57**, 64–9 (1955)

33. Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., Yamada, H., and Tomizawa, K., *Endocrinol. Japon.*, **2,** 183–88 (1955)
34. Benson, G. K., and Folley, S. J., *Nature*, **177,** 700 (1956)
35. Jöchle, W., *Endokrinologie*, **33,** 190–4 (1956)
36. Gaupp, V., and Spatz, H., *Acta Neurovegetativa*, **12,** 285–328 (1955)
37. Metuzals, J., *Z. Zellforsch. u. Mikroskop. Anat.*, **43,** 319–34 (1955)
38. Hough, W. H., Bearden, H. J., and Hansel, W., *J. Animal Sci.*, **14,** 739–45 (1955)
39. Everett, J. W., Sawyer, C. H., and Markee, J. E., *Endocrinology*, **44,** 234–50 (1949)
40. Barraclough, C. A., and Sawyer, C. H., *Endocrinology*, **57,** 329–37 (1955)
41. Barraclough, C. A., *Anat. Record*, **124,** 255 (1956)
42. Whitelaw, J., *J. Clin. Endocrinol. Metabolism*, **16,** 972 (1956)
43. Sawyer, C. H., Critchlow, B. V., and Barraclough, C. A., *Endocrinology*, **57,** 345–54 (1955)
44. Munson, P. L., and Briggs, F. N., *Recent Progr. Hormone Research*, **11,** 83–118 (1955)
45. Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., Yamada, H., and Tomizawa, K., *Endocrinol. Japon.*, **2,** 189–94 (1955)
46. Sulman, F. G., and Winnik, H. Z., *Lancet*, **I,** 161–62 (1956)
47. Marshall, W. K., and Leiberman, D. M., *Lancet*, **I,** 162 (1956)
48. Chambon, Y., *Ann. endocrinol.* (*Paris*), **16,** 912–22 (1955)
49. Fraps, R. M., and Fevold, H. L., *Proc. Soc. Exptl. Biol. Med.*, **90,** 440–46 (1955)
50. Donovan, B. T., and Harris, G. W., *J. Physiol.* (*London*), **131,** 102–14 (1956)
51. Donovan, B. T., and van der Werff ten Bosch, J. J., *J. Physiol.* (*London*), **132,** 123–29 (1956)
52. Jöchle, W., *Endokrinologie*, **33,** 129–38 (1956)
53. Denison, M. E., and Zarrow, M. X., *Proc. Soc. Exptl. Biol. Med.*, **89,** 632–34 (1955)
54. Dutt, R. H., and Bush, L. F., *J. Animal Sci.*, **14,** 885–96 (1955)
55. van der Lee, S., and Boot, L. M., *Excerpta Med. Sect. III*, **10,** 551 (1956)
56. Domanowsky, K., and Wieser, S., *Z. ges. exptl. Med.*, **126,** 496–503 (1955)
57. Michael, S. T., *Psychiat. Quart.*, **30,** 63–72 (1956)
58. Wilhelmi, A. E., Pickford, G. E., and Sawyer, W. H., *Endocrinology*, **57,** 243–52 (1955)
59. Saeki, Y., and Tanabe, Y., *Poultry Sci.*, **34,** 909–19 (1955)
60. Koller, G., *Zoöl. Anz.*, Suppl. **19,** 123–32 (1956)
61. Karli, P., *Compt. rend. soc. biol.*, **149,** 2245–47 (1955)
62. Riss, W., Valenstein, E. S., Sinks, J., and Young, W. C., *Endocrinology*, **57,** 139–46 (1955)
63. Byrnes, W. W., and Shipley, E. G., *Endocrinology*, **57,** 5–9 (1955)
64. Soulairac, A., Teysseyre, J., and Soulairac, M. L., *Ann. endocrinol.* (*Paris*), **16,** 694–701 (1955)
65. Pauker-Warren, R., and Aronson, L. R., *Endocrinology*, **58,** 293–304 (1956)
66. Beach, F. A., Zitrin, A., and Jaynes, J., *J. Exptl. Zoöl.*, **130,** 381–401 (1955)
67. Green, J. D., (Personal communication 1956)
68. Cowie, A. T., and Folley, S. J., *The Hormones*, **3,** 309–87 (1955)
69. Herlant, M., *Arch. Biol.* (*Liége*), **67,** 89–180 (1956)
70. Knigge, K. M., *Endocrinology*, **57,** 719–29 (1955)

71. Ladman, A. J., and Barrnett, R. J., *J. Morphol.*, **98**, 205–21 (1956)
72. Hoogstra, M. J., and de Jongh, S. E., *Acta Physiol. Pharmacol. Neerl.*, **4**, 145–52 (1955)
73. Simpson, M. E., van Wagenen, G., and Carter, F., *Proc. Soc. Exptl. Biol. Med.*, **91**, 6–11 (1956)
74. Grieser, K. C., and Browman, L. G., *Endocrinology*, **58**, 206–11 (1956)
75. Hoogstra, M. J., and Paesi, F. J. A., *Acta Physiol. Pharmacol. Neerl.*, **4**, 395–406 (1955)
76. Schulze, H. F. A., *Z. mikroskop. anat. Forsch.*, **61**, 420–48 (1955)
77. Everett, J. W., *Endocrinology*, **58**, 786–96 (1956)
78. Clifton, K. H., and Meyer, R. K., *Endocrinology*, **58**, 681–85 (1956)
79. Meyer, R. K., and Clifton, K. H., *Arch. Biochem. and Biophys.*, **62**, 198–209 (1956)
80. Meyer, R. K., and Clifton, K. H., *Endocrinology*, **58**, 686–93 (1956)
81. Clifton, K. H., and Meyer, R. K., *Anat. Record*, **125**, 65–81 (1956)
82. Segal, S. J., and Thompson, C. R., *Proc. Soc. Exptl. Biol. Med.*, **91**, 623–5 (1956)
83. Sanfilippo, G., *Chem. Abstracts*, **50**, 7323e (1956)
84. Melloni, G., and Genesi, M., *Chem. Abstracts*, **50**, 280 (1956)
85. Vimeux, J., *Compt. rend. soc. biol.*, **149**, 2151–53 (1955)
86. Das, B. C., and Nalbandov, A. V., *Endocrinology*, **57**, 705–10 (1955)
87. Eto. T., and Imamichi, T., *Endocrinol. Japon.*, **2**, 149–54 (1955)
88. Behrman, S. J., and Niemann, P., *Fertil. Steril.*, **6**, 415–21 (1955)
89. Donato, L., Turchetti, G., and Zacutti, A., *Folia Endocrinol. (Pisa)*, **8**, 569–76 (1955)
90. Sakiz, E., *Compt. rend. soc. biol.*, **149**, 1744–46 (1955)
91. Drescher, J., and Stange, H.-H., *Acta Endocrinol.*, **19**, 289–96 (1955)
92. Johnsen, S. G., *Acta Endocrinol.*, **20**, 101–11 (1955)
93. Butt, W. R., *J. Endocrinol.*, **13**, 167–77 (1956)
94. Brown, P. S., *J. Endocrinol.*, **13**, 59–64 (1955)
95. Brown, P. S., *J. Endocrinol.*, **13**, 178–84 (1956)
96. Schneider, W. G., and Frahm, H., *Acta Endocrinol.*, **20**, 279–92 (1955)
97. Stolte, L. A. M., Bakker, J. H. J., and Verboom, E., *Acta Endocrinol.*, **20**, 93–100 (1955)
98. van Gilse, H. A., Nass, C. A. G., and Kassenaar, A. A. H., *Acta Endocrinol.*, **21**, 19–31 (1956)
99. Suehiro, M., Kidokoro, M., and Sato, T., *Endocrinol. Japon.*, **2**, 175–82 (1955)
100. Chance, M. R. A., *Nature*, **177**, 228–29 (1956)
101. Paesi, F. J. A., de Jongh, S. E., and Hoogstra, M. J., *Acta Physiol. Pharmacol. Neerl.*, **4**, 445–53 (1956)
102. Diczfalusy, E., and Heinrichs, H. D., *Arch. Gynäkol.*, **187**, 556–94 (1956)
103. Sani, G., *Excerpta Med. Sect. III.*, **10**, 554a (1956)
104. Soliman, F. A., and Badawi, H. M., *Nature*, **177**, 235 (1956)
105. Brown-Grant, K., *J. Phyisol. (London)*, **131**, 70–84 (1956)
106. Flury, E., and Berger, J., *Gynaecologia*, **140**, 250–58 (1955)
107. Ortiz, E., *Anat. Record.* **122**, 517–37 (1955)
108. Mandl, A. M., and Zuckerman, S., *J. Endocrinol.*, **13**, 243–68 (1956)
109. Bastian, J. W., and Zarrow, M. X., *Poultry Sci.*, **34**, 776–88 (1955)
110. Allende, I. L. C., de, *Am. J. Anat.*, **98**, 293–305 (1956)

111. Gilbert, C., and Gillman, J., *Endocrinology*, **58**, 753–66 (1956)
112. Bartelmez, G. W., *Am. J. Anat.*, **98**, 69–95 (1956)
113. Payne, H. W., and Latour, J. P. A., *J. Clin. Endocrinol. Metabolism*, **15**, 1106–15 (1955)
114. Maengwyn-Davies, G. D., and Weiner, R., *J. Clin. Endocrinol. Metabolism*, **15**, 1150–52 (1955)
115. Sulak, B., and Zimmermann, W., *Acta Endocrinol.*, **19**, 213–16 (1955)
116. Patzelt, V., *Z. mikroskop. anat. Forsch.*, **61**, 309–59 (1955)
117. Fetzer, S., Hillebrecht, J., Muschke, H. E., and Tonutti, E., *Z. Zellforsch. u. Mikroskop. Anat.*, **43**, 404–20 (1955)
118. Herrmann, M., *Endokrinologie*, **33**, 139–50 (1956)
119. Knigge, K. M., and Leathem, J. H., *Anat. Record*, **124**, 679–707 (1956)
120. Steur, M., Paesi, F. J. A., and de Jongh, S. E., *Acta Physiol. Pharmacol. Neerl.*, **4**, 359–70 (1955)
121. Burkl, W., *Z. Zellforsch. u. Mikroskop. Anat.*, **43**, 345–82 (1955)
122. Green, S. H., Smith, A. U., and Zuckerman, S., *J. Endocrinol.*, **13**, 330–34 (1956)
123. Payne, R. W., and Hellbaum, A. A., *Endocrinology*, **57**, 193–99 (1955)
124. Odor, L. D., *Am. J. Anat.*, **97**, 461–91 (1955)
125. Blandau, R. J., *Fertil. Steril.*, **6**, 391–404 (1955)
126. Barraclough, C. A., *Am. J. Anat.*, **97**, 493–521 (1955)
127. Allende, I. L. C. de, and Orías, O., *Acta Physiol. Latinoamer.*, **5**, 57–84 (1955)
128. Lever, J. D., *Anat. Record.*, **124**, 111–18 (1956)
129. Dawson, A. B., and Velardo, J. T., *Am. J. Anat.*, **97**, 303–29 (1955)
130. Moore, W. W., and Nalbandov, A. V., *J. Endocrinol.*, **13**, 18–25 (1955)
131. Corner, G. W., Jr., *Am. J. Anat.*, **98**, 377–401 (1956)
132. Westman, A., *Acta Obstet. Gynecol. Scand.*, **34**, 92–104 (1955)
133. Scott, R. B., *Fertil. Steril.*, **7**, 45–56 (1956)
134. Leckie, F. H., *J. Obstet. Gynaecol. Brit. Empire*, **62**, 542–7 (1955)
135. Parkes, A. S., *J. Endocrinol.*, **13**, 201–10 (1956)
136. Deanesly, R., *J. Endocrinol.*, **13**, 211–20 (1956)
137. Kullander, S., *Acta Endocrinol.*, **21**, 204–10 (1956)
138. Kullander, S., *Acta Endocrinol.*, **21**, 65–76 (1956)
139. Desclin, L., *Compt. rend. soc. biol.*, **149**, 2017–20 (1955)
140. Takewaki, K., *J. Fac. Sci., Univ. Tokyo*, **7**, 465–75 (1955)
141. Macintyre, M. N., *Anat. Record*, **124**, 27–45 (1956)
142. Balmain, J. H., Biggers, J. D., and Claringbold, P. J., *Australian J. Biol. Sci.*, **9**, 147–58 (1956)
143. West, T. C., and Cervoni, P., *Am. J. Physiol.*, **182**, 287–91 (1955)
144. Warbrick, J. G., *J. Embryol. Exptl. Morphol.*, **3**, 256–64 (1956)
145. Snell, R. S., and Nicol, T., *J. Obstet. Gynaecol. Brit. Empire*, **62**, 572–73 (1955)
146. Warbrick, J. G., *Quart. J. Micro. Sci.*, **97**, 11–15 (1956)
147. Hadek, R., *Quart. J. Micro .Sci.*, **96**, 489–93 (1955)
148. Augustin, E., and Moser, A., *Arch. Gynäkol.*, **185**, 759–80 (1955)
149. Augustin, E., and Huwald, R., *Arch. Gynäkol.*, **187**, 406–25 (1956)
150. Lutwak-Mann, C., *J. Endorcinol.*, **13**, 26–38 (1955)
151. Takeuchi, T., Higashi, K., and Watanuki, S., *J. Histochem. Cytochem.*, **3**, 485–91 (1955)
152. Hanon, F., and Coquoin-Carnot, M., *Compt. rend. soc. biol.*, **149**, 2126–28 (1955)

153. Gelfant, S., and Clemmons, J. J., *J. Cellular Comp. Physiol.*, **46**, 529–39 (1955)
154. Borell, U., Nilsson, O., Wersäll, J., and Westman, A., *Acta Obstet. Gynecol. Scand.*, **35**, 35–41 (1956)
155. Bahr, G. F., and Moberger, G., *Z. Geburtshilfe u. Gynäkol.*, **146**, 33–42 (1956)
156. Melton, C. E., Jr., *Endocrinology*, **58**, 139–49 (1956)
157. Diczfalusy, E., and Westman, A., *Acta Endocrinol.*, **21**, 321–36 (1956)
158. Diczfalusy, E., Borell, U., Magnusson, A.-M., and Westman, A., *Acta Endocrinol.*, Suppl. 24, 51 pp. (1956)
159. Waidl, E., *Endokrinologie*, **32**, 147–48 (1955)
160. Valcourt, A. J., Thayer, S. A., Doisy, E. A., Jr., Elliott, W. H., and Doisy, E. A., *Endocrinology*, **57**, 692–99 (1955)
161. Kinsella, R. A., Francis, F. E., Thayer, S. A., and Doisy, E. A., *J. Biol. Chem.*, **219**, 265–72 (1956)
162. Szego, C. M., *Endocrinology*, **57**, 541–49 (1955)
163. Reiher, K. H., *Endokrinologie*, **33**, 60–63 (1955)
164. Koch, W., and Heim, G., *Endokrinologie*, **32**, 148–52 (1955)
165. Kalman, S. M., *J. Pharmacol. Exptl. Therap.*, **115**, 442–48 (1955)
166. Mueller, G. C., and Herranen, A., *J. Biol. Chem.*, **219**, 585–94 (1956)
167. Schuck, J., and Blasius, R., *Klin. Wochschr.*, **33**, 1093–95 (1955)
168. Hurley, L. S., and Herrmann, H., *Am. J. Physiol.*, **183**, 67–70 (1955)
169. Anselmi, F., Della-Bella, D., and Genovese, E., *Chem. Abstracts*, **50**, 8884b (1956)
170. Dirscherl, W., Schriefers, H., and Breuer, H., *Acta Endocrinol.*, **20**, 181–91 (1955)
171. Bever, A. T., Velardo, J. T., and Hisaw, F. L., *Endocrinology*, **58**, 512–22 (1956)
172. Bullough, W. S., *Vitamins and Hormones*, **13**, 261–92 (1955)
173. Schofield, B. M., *J. Physiol. (London)*, **129**, 289–304 (1955)
174. Velardo, J. T., and Sturgis, S. H., *Proc. Soc. Exptl. Biol. Med.*, **90**, 609–10 (1955)
175. Velardo, J. T., and Sturgis, S. H., *Proc. Soc. Exptl. Biol. Med.*, **90**, 181–83 (1955)
176. Velardo, J. T., and Sturgis, S. H., *Am. J. Physiol.*, **183**, 259–60 (1955)
177. Velardo, J. T., and Sturgis, S. H., *J. Clin. Endocrinol. Metabolism*, **16**, 496–506 (1956)
178. Huggins, C., and Jensen, E. V., *J. Exptl. Med.*, **102**, 335–60 (1955)
179. Huggins, C., *Proc. Soc. Exptl. Biol. Med.*, **92**, 304–5 (1956)
180. Breneman, W. R., *Endocrinology*, **58**, 262–71 (1956)
181. Tullner, W. W., and Hertz, R., *Endocrinology*, **58**, 282–83 (1956)
182. Kline, I. T., *Endocrinology*, **57**, 120–28 (1955)
183. Penhos, J. C., *Acta Physiol. Latinoamer.*, **5**, 22–30 (1955)
184. Krohn, P. L., *J. Anat.*, **89**, 269–82 (1955)
185. Zander, J., *Klin. Wochschr.*, **33**, 697–701 (1955)
186. Kaufmann, C., and Zander, J., *Klin. Wochschr.*, **34**, 7–9 (1956)
187. Westphal, U., *Endocrinology*, **57**, 456–65 (1955)
188. Trolle, D., *Acta Endocrinol.*, **19**, 363–85 (1955)
189. Feyel-Cabanes, T., *Compt. rend. soc. biol.*, **149**, 1746–9 (1955)
190. Hertz, R., and Tullner, W. W., *Proc. Soc. Exptl. Biol. Med.*, **91**, 76–78 (1956)
191. Hertz, R., Waite, J. H., and Thomas, L. B., *Proc. Soc. Exptl. Biol. Med.*, **91**, 418–20 (1956)
192. Davis, M. E., and Wied, G. L., *J. Clin. Endocrinol. Metabolism*, **15**, 923–30 (1955)

193. Mardones, E., Jadrijevic, D., and Lipschutz, A., *Nature*, **177**, 478–79 (1956)
194. Mardones, E., Iglesias, R., and Lipschutz, A., *Endocrinology*, **58**, 212–19 (1956)
195. Hall, K., *J. Endocrinol.*, **12**, 247–51 (1955)
196. Crelin, E. S., and Levin, J., *Endocrinology*, **57**, 730–47 (1955)
197. Ganschow, R. E., *Growth*, **19**, 165–68 (1955)
198. Wada, H., and Yuhara, M., *Chem. Abstracts*, **50**, 6622e (1956)
199. Eichner, E., Waltner, C., Goodman, M., and Post, S., *Am. J. Obstet. Gynecol.*, **71**, 1035–48 (1956)
200. Noall, M. W., and Frieden, E. H., *Endocrinology*, **58**, 659–64 (1956)
201. Zuckerman, S., *Nature*, **177**, 58–60 (1956)
202. Wiesner, B. P., and Yudkin, J., *Nature*, **176**, 249–50 (1955)
203. East, J., *J. Endocrinol.*, **12**, 252–76 (1955)
204. East, J., *J. Endocrinol.*, **13**, 94–100 (1955)
205. Loeser, A., and Mikulicz, K., *Klin. Wochschr.*, **33**, 1017–20 (1955)
206. Schuster, A., *Arch. Gynäkol.*, **187**, 231–42 (1955)
207. Magendie, M. J., Bernard, I., Boussemart, E., and Martin, G., *Ann. endocrinol. (Paris)*, **16**, 69–76 (1955)
208. Lindahl, P. E., Ingelman-Sundberg, A., Furuhjelm, M., and Nilsson, A., *J. Obstet. Gynaecol. Brit. Empire*, **63**, 363–71 (1956)
209. Schwartz, R., and Zinsser, H. H., *Fertil. Steril.*, **6**, 450–58 (1955)
210. Hübner, K. A., *Zentr. Gynäkol.*, **77**, 1220–29 (1955)
211. Dauzier, L., *Compt. rend. soc. biol.*, **149**, 1872–74 (1955)
212. Dauzier, L., *Compt. rend. soc. biol.*, **149**, 1941–43 (1955)
213. Rowson, L. E., *Brit. Veterinary J.*, **111**, 334–42 (1955)
214. Adams, C. E., *J. Endocrinol.*, **13**, 296–308 (1956)
215. Du Mesnil du Buisson, F., and Dauzier, L., *Ann. endocrinol. (Paris)*, **16**, 413–22 (1955)
216. Symposium on Physiology of Fertilization, Palermo, *Exptl. Cell Research*, **10**, 257–393 (1956)
217. Austin, C. R., *Exptl. Cell Research*, **10**, 533–40 (1956)
218. Strauss, F., *J. Embryol. Exptl. Morphol.*, **4**, 42–56 (1956)
219. Edwards, R. G., and Sirlin, J. L., *Nature*, **177**, 429 (1956)
220. Fridhandler, L., Hafez, E. S. E., and Pincus, G., *Proc. Soc. Exptl. Biol. Med.*, **92**, 127–29 (1956)
221. Gates, A. H., *Nature*, **177**, 754–55 (1956)
222. Whitten, W. K., *Nature*, **177**, 96 (1956)
223. Averill, R. L. W., Adams, C. E., and Rowson, L. E. A., *Nature*, **176**, 167–68 (1955)
224. Hertig, A. T., Rock, J., and Adams, E. C., *Am. J. Anat.*, **98**, 435–93 (1956)
225. Wislocki, G. B., and Dempsey, E. W., *Anat. Record.*, **123**, 133–67 (1955)
226. Ortmann, R., *Z. Anat. u. Entwicklungsgeschichte*, **119**, 28–54 (1955)
227. Thomsen, K., *Chem. Abstracts*, **50**, 5125c (1956)
228. Thomsen, K., *Chem. Abstracts*, **50**, 5125g (1956)
229. Rodway, H. E., and Marsh, F., *J. Obstet. Gynaecol. Brit. Empire*, **63**, 111–15 (1956)
230. Wislocki, G. B., and Dempsey, E. W., *Anat. Record*, **123**, 33–63 (1955)
231. Davies, J., *J. Anat.*, **90**, 135–42 (1956)
232. Metcalfe, J., Romney, S. L., Ramsey, L. H., Reid, D. E., and Burwell, C. S., *J. Clin. Invest.*, **34**, 1632–38 (1955)

233. Eliasson, R., Åström, A., *Acta Pharmacol. Toxicol.*, **11**, 254–64 (1955)
234. Crawford, J. M., and Fraser, A., *J. Obstet. Gynaecol. Brit. Empire*, **62**, 896–98 (1955)
235. Crawford, J. M., *J. Obstet. Gynaecol. Brit. Empire*, **63**, 87–90 (1956)
236. Reynolds, S. R. M., and Paul, W. M., *Bull. Johns Hopkins Hosp.*, **97**, 383–94 (1955)
237. Spanner, R., *Am. J. Obstet. Gynecol.*, **71**, 350–62 (1956)
238. Ramsey, E. M., *Am. J. Anat.*, **98**, 159–89 (1956)
239. Alexander, D. P., Andrews, R. D., Huggett, A. St. G., Nixon, D. A., and Widdas, W. F., *J. Physiol. (London)*, **129**, 352–66 (1955)
240. Alexander, D. P., Huggett, A. St. G., Nixon, D. A., and Widdas, W. F., *J. Physiol. (London)*, **129**, 367–83 (1955)
241. Holmberg, N. G., Kaplan, B., Karvonen, M. J., Lind, J., and Malm, M., *Acta Physiol. Scand.*, **36**, 291–99 (1956)
242. Cahn, T., and Houget, J., *J. Physiol. (Paris)*, **47**, 835–48 (1955)
243. Barron, D. H., and Battaglia, F. C., *Yale J. Biol. Med.*, **28**, 197–207 (1955–56)
244. Feaster, J. P., Hansard, S. L., Outler, J. C., and Davis, G. K., *J. Nutrition*, **58**, 399–406 (1956)
245. Feltman, R., and Kosel, G., *Science*, **122**, 560–61 (1955)
246. Halliday, R., *Proc. Roy. Soc. (London)*, [B] **144**, 427–30 (1955)
247. Brambell, F. W. R., and Halliday, R., *Proc. Roy. Soc. (London)*, [B] **145**, 170–78 (1956)
248. Jöchle, W., *Endokrinologie*, **33**, 63–69 (1955)
249. Stucki, J. C., and Meyer, R. K., *Endocrinology*, **57**, 173–80 (1955)
250. Hagopian, M., Pincus, G., Carlo, J., and Romanoff, E. B., *Endocrinology*, **58**, 387–88 (1956)
251. Levitz, M., Condon, G. P., and Dancis, J., *Endocrinology*, **58**, 376–80 (1956)
252. Hon, E. H., and Morris, J. McL., *Am. J. Obstet. Gynecol.*, **71**, 331–41 (1956)
253. Penhos, J. C., and Cardeza, A. F., *Compt. rend. soc. biol.*, **149**, 1796 (1955)
254. Fried, P. H., and Rakoff, A. E., *Obstet. Gynecol.*, **6**, 12–17 (1955)
255. Creutzberg, F., *Acta Endocrinol.*, **19**, 386–96 (1955)
256. Cheval, M., and Hans, M. J., *Bruxelles Méd.*, **35**, 1685–1708; 1740–46 (1955)
257. Takano, H., *Japan J. Physiol.*, **6**, 22–28 (1956)
258. Kawakami, M., *Japan. J. Physiol.*, **5**, 251–73 (1955)
259. van Wagenen, G., and Simpson, M. E., *Proc. Soc. Exptl. Biol. Med.*, **90**, 346–48 (1955)
260. Hafez, E. S. E., and Pincus, G., *Proc. Soc. Exptl. Biol. Med.*, **91**, 531–34 (1956)
261. Csapo, A., *Am. J. Anat.*, **98**, 273–91 (1956)
262. Denamur, R., and Martinet, J., *Compt. rend. soc. biol.*, **149**, 2105–7 (1955)
263. Alexander, D. P., Frazer, J. F. D., and Lee, J., *J. Physiol. (London)*, **130**, 148–55 (1955)
264. Corrêa Freire, J. R., *Biol. Abstracts*, **30**, 13413–15 (1956)
265. Augustin, E., and Rothe, G., *Z. Geburtshilfe u. Gynäkol.*, **145**, 159–71 (1956)
266. Chambon, Y., *Compt. rend. soc. biol.*, **149**, 2164–67 (1955)
267. Simonnet, H., Robey, M., and Piaux, G., *Excerpta Med. Sect. III*, **10**, 555 (1956)
268. Piaux, G., Robey, M., and Simonnet, H., *Excerpta Med., Sect. III*, **10**, 556 (1956)
269. Frazer, J. F. D., *J. Embryol. Exptl. Morphol.*, **3**, 332–34 (1955)

270. Böving, B. G., *Am. J. Anat.*, **98**, 403–34 (1956)
271. Ladman, A. J., *Anat. Record*, **125**, 41–53 (1956)
272. Whitten, W. K., *J. Endocrinol.*, **13**, 1–6 (1955)
273. Canivenc, R., and Mayer, G., *Ann. endocrinol. (Paris)*, **16**, 1–33 (1955)
274. Canivenc, R., and Mayer, G., *Compt. rend. Acad. Sci. (Paris)*, **240**, 2348–50 (1955)
275. Canivenc, R., Radenac, J., and Mayer, G., *Compt. rend. soc. biol.*, **149**, 1258–60 (1955)
276. Meunier, J. M., and Mayer, G., *Compt. rend. soc biol.*, **149**, 1263–65 (1955)
277. Sulman, F. G., *Excerpta Med., Sect. III*, **10**, 560 (1956)
278. Shelesnyak, M. C., and Davies, A. M., *Proc. Soc. Exptl. Biol. Med.*, **89**, 629–32 (1955)
279. Stamler, F. W., *Proc. Soc. Exptl. Biol. Med.*, **90**, 294–98 (1955)
280. Walker, D. G., and Wirtschafter, Z. T., *J. Nutrition*, **58**, 147–73 (1956)
281. Dobson, W. G., and Gornall, A. G., *Am. J. Obstet. Gynecol.*, **72**, 70–74 (1956)
282. Dewhurst, C. J., *Lancet*, **I**, 471–72 (1956)
283. James, F., *Lancet*, **I**, 202–3 (1956)
284. Makowski, E. L., Prem, K. A., and Kaiser, I. H., *Science*, **123**, 542–43 (1956)
285. Sachs, L., Serr, D. M., and Danon, M., *Science*, **123**, 548 (1956)
286. Shettles, L. B., *Am. J. Obstet. Gynecol.*, **71**, 834–38 (1956)
287. Soiva, K., and Parviainen, S., *Acta Endocrinol.*, **20**, 161–68 (1955)
288. Mastboom, J. L., and Horsten, G. P. M., *Gynaecologia*, **141**, 129–35 (1956)
289. Franklin, K. J., and Winstone, N. E., *J. Obstet. Gynaecol. Brit. Empire*, **62**, 29–36 (1955)
290. Mack, H. C., *The Plasma Proteins in Pregnancy* (Charles C Thomas, Springfield, Ill., 118 pp., 1955)
291. Hoffmann, F., and Uhde, G., *Zentr. Gynäkol.*, **77**, 1909–13 (1955)
292. Varangot, J., Seeman, A., Cedard, L., and Guiguet, C., *Compt. rend. soc. biol.*, **149**, 1764–69 (1955)
293. Semm, K., *Klin. Wochschr.*, **33**, 817–18 (1955)
294. Pritchard, J. A., and Ratnoff, O. D., *Surg. Gynecol. Obstet.*, **101**, 467–77 (1955)
295. MacKinnon, P. C. B., and MacKinnon, I. L., *J. Obstet. Gynaecol. Brit. Empire*, **62**, 626–28 (1955)
296. Brown, J. B., *Lancet*, **I**, 704–7 (1956)
297. Hon, E. H., and Morris, J. M. L., *Surg. Gynecol. Obstet.*, **101**, 59–62 (1955)
298. Venning, E. H., and Dyrenfurth, I., *J. Clin. Endocrinol. Metabolism*, **16**, 426–28 (1956)
299. Plotz, E. J., and Davis, M. E., *Acta Endocrinol.*, **21**, 259–67 (1956)
300. Davis, M. E., and Plotz, E. J., *Acta Endocrinol.*, **21**, 245–58 (1956)
301. Yamamoto, H., and Turner, C. W., *Proc. Soc. Exptl. Biol. Med.*, **92**, 130–32 (1956)
302. Smith, T. C., *Endocrinology*, **57**, 33–43 (1955)
303. Richardson, F. L., *Anat. Record*, **123**, 279–89 (1955)
304. Benson, G. K., Cowie, A. T., Cox, C. P., Flux, D. S., and Folley, S. J., *J. Endocrinol.*, **13**, 46–58 (1955)
305. Mayer, G., and Duluc, A. J., *Arch. Sci. Physiol. (Paris)*, **9**, 97–114 (1955)
306. Johnson, R. M., and Meites, J., *Proc. Soc. Exptl. Biol. Med.*, **89**, 455–58 (1955)
307. Chen, T. T., Johnson, R. E., Lyons, W. R., Li, C. H., and Cole, R. D., *Endocrinology*, **57**, 153–57 (1955)

308. Ferguson, D. J., *Surgery*, **39**, 30–36 (1956)
309. Mizuno, H., Iida, K., and Naito, M., *Endocrinol. Japon.*, **2**, 163–69 (1955)
310. Ringler, I., and Nelson, W. L., *Endocrinology*, **57**, 231–35 (1955)
311. Tuba, J., Orr, P. F., and Wiberg, G. S., *Canadian J. Biochem. Physiol.*, **33**, 904–8 (1955)
312. Bang, F. B., Vellisto, I., and Libert, R., *Bull. Johns Hopkins Hosp.*, **98**, 255–85 (1956)
313. Howe, A., Richardson, K. C., and Birbeck, M. S. C., *Exptl. Cell Research*, **10**, 194–213 (1956)
314. Williams, W. J., and Turner, C. W., *Proc. Soc. Exptl. Biol. Med.*, **90**, 531–33 (1955)
315. Eayrs, J. T., and Baddeley, R. M., *J. Anat.*, **90**, 161–71 (1956)
316. *The Hypophyseal Growth Hormone, Nature and Actions, Henry Ford Hospital Symposium* (Smith, R. W., Gaebler, O. H., and Long, C. N. H., (Eds.), The Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y., 576 pp., 1955)
317. Clermont, Y., and Morgenthaler, H., *Endocrinology*, **57**, 369–82 (1955)
318. Lison, L., *Acta Histochemica*, **2**, 47–67 (1955)
319. Horn, E. H., *Endocrinology*, **57**, 399–408 (1955)
320. Wolf, R. C., and Leathem, J. H., *Endocrinology*, **57**, 286–90 (1955)
321. Kaufman, N., Klavins, J. V., and Kinney, T. D., *Am. J. Pathol.*, **32**, 105–15 (1956)
322. Payne, J. M., *J. Pathol. Bact.*, **71**, 117–23 (1956)
323. Oakberg, E. F., *J. Morphol.*, **97**, 39–54 (1955)
324. Bryan, J. H. D., and Gowen, J. W., *Biol. Bull.*, **110**, 229–42 (1956)
325. Pařízek, J., and Záhoř, Z., *Nature*, **177**, 1036–37 (1956)
326. Kar, A. B., Roy, S. K., and Roy, A. C., *Chem. Abstracts*, **50**, 7308i (1956)
327. Roy, S. N., Kar, A. B., and Datta, S. N., *Chem. Abstracts*, **50**, 8885f (1956)
328. Bacon, R. L., and Kirkman, H., *Endocrinology*, **57**, 255–71 (1955)
329. Coombs, C. J. F., and Marshall, A. J., *J. Endocrinol.*, **13**, 107–11 (1956)
330. Lofts, B., and Marshall, A. J., *J. Endocrinol.*, **13**, 101–6 (1956)
331. Conti, C., Marinosci, A., Ippolito, A., Ricci, P. D., and Mazzuoli, G. F., *Folia Endocrinol. (Pisa)*, **8**, 709–44 (1955)
332. Erb, R. E., Flerchinger, F. H., Ehlers, M. H., and Gassner, F. X., *J. Dairy Sci.*, **39**, 326–38 (1956)
333. Hopwood, M. L., Rutherford, E. R., and Gassner, F. X., *J. Dairy Sci.*, **39**, 51–59 (1956)
334. Tyler, E. T., and Singher, H. O., *J. Am. Med. Assoc.*, **160**, 91–97 (1956)
335. Hamilton, J. B., Bunch, L. D., Mestler, G. E., and Imagawa, R., *J. Clin. Endocrinol. Metabolism*, **16**, 301–21 (1956)
336. Charny, C. W., *J. Am. Med. Assoc.*, **160**, 98–101 (1956)
337. Kearns, W. M., *J. Urol.*, **75**, 852–56 (1956)
338. Mann, T., Leone, E., and Polge, C., *J. Endocrinol.*, **13**, 279–90 (1956)
339. Mann, T., Polge, C., and Rowson, L. E. A., *J. Endocrinol.*, **13**, 133–40 (1956)
340. Kellerman, G. M., *Australian J. Exptl. Biol.*, **33**, 579–92 (1955)
341. Aitken, R. N. C., *J. Anat.*, **89**, 430–39 (1955)
342. Levey, H. A., and Szego, C. M., *Am. J. Physiol.*, **182**, 507–12 (1955)
343. Dorfman, R. I., and Shipley, R. A., *Androgens* (John Wiley & Sons, Inc., New York, N. Y., 590 pp., 1956)

344. Glover, T. D., *J. Endocrinol.*, **13**, 235–42 (1956)
345. Raboch, J., and Záhoř, Z., *Endokrinologie*, **33**, 160–69 (1956)
346. Migeon, C. J., *J. Biol. Chem.*, **218**, 941–44 (1956)
347. Levedahl, B. H., *Arch. Biochem. and Biophys.*, **59**, 300–1 (1955)
348. Schneider, W., *Arch. Exptl. Pathol. u. Pharmakol.*, **227**, 169–76 (1955)
349. McDonald, J. H., and Heckel, N. J., *J. Urol.*, **75**, 527–29 (1956)
350. Arambarri, M. L., *Z. ges. exptl. Med.*, **127**, 227–35 (1956)
351. Baumann, W., *Z. ges. exptl. Med.*, **126**, 116–24 (1955)
352. Bloch, E., Benirschke, K., and Rosemberg, E., *Endocrinology*, **58**, 626–33 (1956)
353. Holmes, W. N., *Anat. Record*, **122**, 271–91 (1955)
354. Benirschke, K., Bloch, E., and Hertig, A. T., *Endocrinology*, **58**, 598–625 (1956)
355. Kochakian, C. D., Tillotson, C., and Endahl, G. L., *Endocrinology*, **58**, 226–31 (1956)
356. Kochakian, C. D., Tillotson, C., Austin, J., Dougherty, E., Haag, V., and Coalson, R., *Endocrinology*, **58**, 315–26 (1956)
357. Korner, A., and Young, F. G., *J. Endocrinol.*, **13**, 78–83 (1955)
358. Korner, A., and Young, F. G., *J. Endocrinol.*, **13**, 84–89 (1955)
359. Korner, A., *J. Endocrinol.*, **13**, 90–93 (1955)
360. Johnsen, S. G., *Acta Endocrinol.*, **21**, 127–76 (1956)

SOMATIC ASPECTS OF THE NERVOUS SYSTEM[1,2,3]

By W. Ross Adey

Department of Anatomy, University of Melbourne, Melbourne, Australia

"Hellenism is to follow, with flexible activity, the whole play of the universal order, to be apprehensive of missing any part of it, of sacrificing one part to another, to slip away from resting in this or that intimation of it, however capital."

Matthew Arnold

Introduction

It is apparent, from a recent symposium (301) containing much of interest about the fascinating roots of neurophysiology, that the very complexity of our special interests within the field may become an increasing barrier to communication within our broad arena. It is therefore refreshing to read Gerard's account (123) of multidisciplinary studies which are signposts, in the problem of cerebral metabolism, to the integration of hitherto uncorrelated knowledge of the parts played by carbohydrate and protein metabolism, of the activities of a variety of supposed humoral transmitter substances, and of even more basic phenomena in ionic transfer through the neuronal membrane.

Additional evidence is available supporting the general concept of spatiotemporal patterning in the nervous system, with the temporal parameter assuming increasing significance. In a penetrating review, Sinclair (282) has examined the doctrine of specific energies in its applications at all levels of the neuraxis and concludes that central structures are well adapted to conduct very varied patterns integral to sensory perception. Unit studies contribute much to our knowledge in this field, and here may be mentioned the investigations of Scheibel *et al.* (270) of convergence patterns in the brainstem reticular formation, and of Green & Machne (137) into unit activity in the hippocampus, and the illuminating observations by Li, Cullen & Jasper of unit behavior in the sensory cortex during activation of specific and nonspecific afferent systems (194, 195). Equally fascinating is the picture of central control over muscle spindle activity noted by Granit *et al.* (133, 134, 135) with the cerebellum mediating its influence through both fast and show pathways arising in the mesencephalic tegmentum.

The pattern of this review follows that of others in recent years, with

[1] This review is based on material available in Australia up to June, 1956. It is not claimed to cover the whole field and indulgence is asked of its many omissions.

[2] The following abbreviations have been used: ATP (adenosine triphosphate), CNS (central nervous system), DFP (diisopropyl fluorophosphate), EEG (electroencephalogram), LSD (lysergic acid diethylamide).

[3] The continued help and encouragement of Professor S. Sunderland is gratefully acknowledged. Nancy Harritt, Vera Purmalis, and Alice Rudolph have rendered invaluable assistance in the preparation of the manuscript.

sequential examination of afferent and efferent mechanisms at various levels.

Peripheral Receptors and Conductors

Somesthesis.—Reviews of cutaneous and special sensory modalities have appeared (32, 271, 282). Sinclair (282) concludes that a spatially and temporally dispersed pattern of impulses leaves the skin and that the physical characteristics of this pattern are the determining factors in the experience of sensory quality and further suggests that there may be no specific fibers and no specific endings. Humoral factors have been studied in relation to both skeletal muscle pain and cutaneous hyperalgesia (84, 144). Responses to temperature change in the lateralis organs and ampullae of the toad are unrelated to the direction of the spatial temperature gradient, contrary to recent theories of spatial gradients in thermal sensibility (228). Reaction times in human responses to thermal stimuli are not necessarily related to conduction velocities (190). Skin temperature is modified by chlorpromazine (65, 298). The structural and functional relationships of Meissner's and Paccinian corpuscles have been studied (51, 259). Firing of proprioceptors occurs at all angles of the cat's knee joint, but individual proprioceptors fire over only a limited range of joint angles (66, 67).

From studies of the fine structure of a variety of nonmyelinated nerves, Hess (154) concludes that during development there are basically different arrangments between Schwann cells and the two essential categories of myelinated and unmyelinated nerve fibers. Large numbers of small (0.1μ) nerve fibers appear as collateral axon sprouts in partly deneurotized nerves within 24 hours of operation, and changes in nucleic acid content have been observed in degeneration and activity (52, 53, 54). The caliber spectra of dental nerves show a single neurite range, peaking at 2 to 3 μ (130).

There is a definite relationship between the time at which a fiber acquires its myelin sheath and the diameter it finally attains (293). Dawson (80) concludes from human evoked potential studies that the sensory afferent fibers from the fingers may have a greater maximum size than the motor fibers to the small muscles of the hand, and are not smaller than afferent fibers from these muscles. Responses *in vivo* from mammalian nerve fibers of low conduction velocity are increased in amplitude up to three times by repetitive stimulation, and this property may be responsible for post-tentaic facilitation in junctional tissues (43). Tasaki (291) has described the initiation and abolition of the action potential at a single node of Ranvier. Changes in length and optical properties follow stimulation of invertebrate nerves (45, 276).

Olfaction.—Ottoson (240) has published the first extensive investigation of the electrical activity of the olfactory epithelium. Electron microscopy of the olfactory nerves indicates a large number of very small fibers (modal diameter 0.2μ) with as many as six million from one side of the pig's nasal

septum (121). Adsorption of odorous substances by the olfactory membrane may be integral to its normal excitation (224). Destruction of the human olfactory nerves is not necessarily followed by loss of appreciation of flavors (63). The finding that centrifugal fibers from prepyriform cortex and adjacent regions can modify electrical activity in the olfactory bulb is a further indication of the importance of central regulation in neural integration of afferent transmission (170).

Visual and auditory receptors.—Much attention is currently directed to the possible physiological basis of color vision (13, 39, 191, 192). Two mechanisms may be involved in color discrimination in the dichromatic yellow-orange-red range and this is supported by theoretical predictions. A statistical information theory of visual thresholds is proposed (138). Histochemical tests have failed to demonstrate carotenoids in the outer segments of rods and cones (107). Granit (132) has described the effects of both centrifugal and antidromic stimulation on the ganglion cells of the retina. Posttetanic potentiation occurs in both cases, but at a higher threshold for centrifugal than for antidromic stimulation. Muscle spindles in the extrinsic eye muscles possess a gamma efferent nerve supply, probably under the influence of retinal and periorbital tissues (74). In the goat, at least, the afferent pathway from the extrinsic ocular muscle spindles is via the trigeminal nerve (308).

Auditory cortical responses following restricted cortical lesions support previous concepts of an orderly frequency distribution within the cochlear receptors (174).

Gustation.—Wide species differences exist in the relative excitability of taste receptors by water, sodium chloride, quinine, and sucrose (21, 68, 245). Application of alkaline solutions to the tongue of the cat results in a general stimulation of several kinds of taste fiber endings (197).

Input to Spinal Cord

The properties of peripheral and central portions of the unmedullated axons of spinal ganglion cells have attracted little attention hitherto. Gasser finds that the compound action potential of peripheral nerves is repeated in dorsal roots, and concludes that root velocities of unmyelinated fibers conform to the size/velocity rule derived from nerve axons (120). Electron microscopy of the nuclear membrane of spinal ganglion cells indicates an arrangement of distributed nodes characteristically present during active nucleocytoplasmic transport (81).

The processes of excitation and inhibition in sensory nerve cells have been studied in Clarke's column of the spinal cord by Laporte and his coworkers (187, 188, 189), and in ingenious invertebrate preparations by Eyzaguirre & Kuffler (96, 97, 186). The giant synapses in Clarke's column (290) add interest to studies of its synaptic organization (200). Laporte concludes that the synaptic arrangment here resembles that in motoneurones

in that there may be reciprocal innervation with inhibition from antagonist muscles, but that the resulting inhibition does not necessitate the interposition of interneurones.

A number of studies have been directed to the origin of the various complexes of the dorsal root reflex, which originates from interaction between afferent fiber terminals and also from interaction between interneurones and the terminals of afferent neurones (42). Slow potentials have been recorded intracellularly in dorsal root fibers in the funiculus of the isolated toad spinal cord (182). A small presynaptic component (Nla) of the negative intermediary cord potential is described (16). Cutaneous, proprioceptive, and bladder representations have been identified in microelectrode studies in the posterior funiculus of the cat (315).

Ascending Pathways in Cord and Brain Stem

Spinal cord.—It has become increasingly apparent that concepts of strictly localized fiber pathways subserving particular modalities in the spinal cord may need revision. Thus Morin has shown by selective cord lesions that fast cutaneous impulses ascend not only in the dorsal funiculi, but also in the ipsilateral lateral funiculus, probably in the dorsal spinocerebellar tract, and that collaterals of these fibers relay in a nucleus of the cervical cord to reach the opposite thalamus and cortex (225). Splanchnic afferents appear to run in the ipsilateral lateral funiculus as well as in the dorsal funiculus (117). Ascending fibers arising in the upper cervical segments of the cord intermingle with those of the corticospinal tract in man and run through the pyramidal decussation into the pons and internal capsule (233). Grundfest and his co-workers have established that the lateral cervical nucleus is a relay station in a major pathway for spinal activation of the olive (27, 185). Some functional regeneration occurs in the cat's spinal cord where transection is followed by administration of a complex bacterial polysaccharide, piromen (272).

Brainstem: specific afferent systems.—The degree to which reflex activity in the extrinsic ocular muscles is to be regarded as independent of cortical control has been reviewed by Whitteridge *et al.* (74, 308) who have confirmed the presence of branches of the trigeminal nerve in these muscles. Optokinetic after-nystagmus is obliterated by light but reappears when the animal is returned to darkness (171).

Central connections of the trigeminal nerve have been tested with particular reference to pain mechanisms and trigeminal neuralgia (26, 17, 176, 177). In addition to classical lemniscal pathways, there are extensive bilateral connections running in the dorsal midbrain and potentials can be recorded widely in the medial regions of thalamus and hypothalamus. A centrifugal influence arising from the spinal nucleus of the trigeminal nerve in the lower medulla can be exaggerated by injection of alumina gel into the spinal nucleus and is accompanied by overreaction to tactile stimulation of the face (177).

From records of binaural interaction at the inferior collicular level, it is clear that some ability to localize sound is possible in the absence of cerebral cortex (265). Vestibular stimulation can inhibit strychnine-induced convulsive activity in the spinal cord through the medullary reticular formation (124).

Brainstem: nonspecific afferent systems.—The accessibility of the central core of grey matter of the brainstem to a wide variety of peripheral sensory stimuli, and the plurality of its own synaptic connections both underline the importance of convergence and interaction studies in an understanding of its role in mechanisms of consciousness. Scheibel *et al.* (270) conclude that convergence is widespread but not unlimited, and that convergence patterns vary markedly in different units. Corticifugal influences were found from sensorimotor cortex but not from auditory cortex. The waking state may be the result of reticular activity maintained by peripheral sensory input, particularly from the peripheral field of the trigeminal nerve, rather than intrinsic in origin (264). Experimental concussion abolishes evoked potentials in the reticular formation, without measurable alteration in lemniscus conduction (105). Behavioral arousal from natural sleep follows stimulation of the central cephalic brain stem in chronic preparations (273). Experimental anatomical studies indicate that ascending axons are restricted to the medial two-thirds of the reticular formation and arise particularly at the levels of the inferior olive and sixth nerve nucleus (40). Evidence is advanced that the activating system is cholinergic and may thus be used for screening antiparkinsonian drugs (155).

Cerebellum.—A new concept of functional localization in the cerebellum is advanced by Chambers & Sprague (55, 56), based on their physiological observations and on the anatomical studies of Jansen & Brodal (165) and stressing the importance of somatic localization in longitudinal efferent corticonuclear strips, rather than the distribution of afferent fibers in cerebellar cortex. The cerebellar cortical discharge induced by strychnine is minimal when recorded along a folium and maximal across a folium (250). The role of pontine structures in the electrical activity of the cerebellum has been tested (142).

Thalamus and Diencephalon

The diffusely projecting thalamic nuclei continue to attract considerable attention, particularly in studies of patterns of thalamocortical activation (241). Cowan & Powell indicate that the midline and intralaminar nuclei, with the exception of the paraventricular nuclei, project to the corpus striatum and adjacent cortex of the medial surface of the hemisphere (75). However, Nashold *et al.* (231) have been unable to discern retrograde degeneration in the thalamus from lesions restricted to caudate nucleus or putamen. Extensive gliosis in reticular and intralaminar nuclei follows additional lesions in the internal capsule.

Microelectrode studies of the effects of barbiturates in the diffusely pro-

jecting thalamic nuclei indicate that the slow waves of the spindle bursts may represent summed positive after-potentials of antecedent groups of spikes (302). The fast cortical rhythms in the initiation of inhalation anesthesia may spring from excitation in the brainstem reticular formation (267).

Secondary cortical discharges from stimulation of widely different levels of the reticular formation reproduce all the features of the secondary cortical discharge obtainable from peripheral stimulation (258). Although stimulation of medial thalamic structures in the cat produces cortical activity resembling human petit mal, it is not possible to define an anatomical entity of origin, nor do the results suggest a diencephalic pacemaker driving a passive cortex (162).

Partial deafferentation of the somatic sensory cortex by damage to its principal thalamic relay nucleus is followed by high amplitude bursts and increased irritability to drugs (284). Li has found that stimulation of a nonspecific thalamic nucleus exerts a facilitatory effect on primary cortical sensory neurones and that this facilitation displays a certain periodicity (193) The optic tract in the cat synapses at four different levels in the lateral geniculate body, and from these levels activity passes to the striate cortex, the lateral nucleus of the thalamus, the pretectal area, and superior colliculus respectively (30). Steady potentials in the lateral geniculate body after repetitive stimulation of the optic nerve are attributable to a steady potential gradient in the geniculate axon (300).

Heath suggests from his studies with implanted electrodes of awareness in humans that a facilitatory pathway runs in the vicinity of the septum and inhibitory effects may arise in more lateral subcortical masses (149).

Cortical Input

Many interesting historical aspects of research in cortical localization are discussed by Jefferson (166). Ontogenetic studies in the cat disclose spatial patterns and temporal sequences of development (141).

Somatic sensory cortex.—The inadequacy of concepts of cortical functions based entirely on spatial localization is exemplified by the findings of Gardner *et al.* (117) that splanchnic afferents project extensively to somatic cortical areas. Penfield & Faulk conclude that the insula represents an extension of the second somatic sensory area previously defined on the superior bank of the Sylvian fissure (242). The second sensory area may be the site of conscious pain perception (28). The plasticity of patterns of sensory representation during development is further underlined by comparison of residual function in cases of hemispherectomy for tumor with results of a similar operation for infantile hemiplegia (118).

The modifications of primary and secondary cortical and thalamic responses to auditory and sciatic stimuli by a painful stimulus suggest that excitation induced by a nociceptive stimulus exerts a prior influence at the subcortical level on ascending sensory system (230). The first surface-positive cortical response to stimulation of the ventrobasal thalamic nucleus is

attributable to activity in thalamocortical fibers and the second to postsynaptic events in cortical cells (243). Unit studies by Li, Cullen & Jasper (194, 195) indicate that the initial surface-positive deflection of the primary evoked potential complex is most likely to be associated with unit firing in layers IV and V of the cortex at the crest of this deflection. By contrast, afferent terminals from nonspecific thalamic pathways appear to terminate widely through many layers of the cortex.

Auditory cortex.—The "masking curve" of threshold intensity for auditory cortical responses in the dog exhibits a more gradual slope on the low-frequency side than on the high-frequency side of the test tone frequencies (297). Human studies indicate a region in the audiogram in the vicinity of 4000 cycles per second where intensity alterations modify perceived pitch (288). Slow potential changes evoked in the auditory cortex of cat and man have been reported (179, 180).

Visual cortex.—Tests of pattern perception following insertion of mica plates into the visual cortex of cats suggest that the animals may have remained largely unaware of widely scattered scotomata (283). Cortical responses evoked by flashing light (206) vary in amplitude and latency according to the color (191). Human subjects experience difficulty in elucidation of hidden-figure color-mosaic cards viewed by a blue-white light flash of short duration (140).

The psychosogenic drug lysergic acid diethylamide (LSD) facilitates evoked primary auditory and visual cortical responses in cats in low concentrations, and at higher concentrations auditory responses are differentially depressed, with continued facilitation of visual responses (257, 268). Visual fits following wounds of the calcarine cortex may be accompanied by lights or formed hallucinations of varying color (269). Discriminatory awareness as measured by the critical flicker fusion threshold is depressed in stutterers as compared with normal adults (64).

Efferent Pathways

Corticospinal projections.—Phillips has recorded with intracellular elecrodes responses in the Betz cells of the cat's motor cortex. Cells on the tonvexity of the gyrus have lower thresholds than those in the depths of the sulcus. With punctate stimulation just strong enough to cause movetment, Betz cells over a radius of 4 mm. are stirred into high-frequency itera -ive firing (246, 247). Chang concludes from microelectrode studies that collaterals of these large pyramidal cell axons may form part of a self-re-exciting cortical circuit (57, 58). The buried cortex in the frontal sulci of the cat possesses a series of motor representations continuous with those on the surface gyri (83) and inhibition of the knee jerk follows stimulation of a restricted area of the cat's motor cortex (235). The lowest thresholds for motor responses with pulse durations of 0.1 to 0.5 msec. occur at stimulus rates of 100 to 250 per seond (216). The relationship between cortical spikes evoked by sensory stimulation and the onset of myoclonus have been studied in

man (305). The termination of the cat's pyramidal tract is restricted to a small region in the ventral part of the dorsal horn of the cord (303).

Nathan & Smith have provided a useful review of present knowledge of the long descending tracts in man (232), and conclude that the Babinski response may or may not follow any lesion of the lateral and ventral columns of the spinal cord, and is often found with histologically normal corticospinal tracts (234). Travis concludes that ablations of the precentral motor area in the macaque do not support the concept that all parts of the motor cortex exert some control over all parts of the body musculature (294, 295). Postcentral and precentral cortical lesions result in persistent lowering of the skin temperature of the contralateral extremities (172).

Subcortical mechanisms in motor functions.—Corticifugal influences may exert their effect at the spinal level through a variety of intermediate stations in the basal ganglia and brainstem reticular formation. Livingston (201) draws attention to modifications in the general level of reticular excitability by psychic factors and emphasizes the part played by corticifugal influences. Experimental anatomical studies indicate widespread connections from the cat's frontal cortex to intralaminar thalamic nuclei, subthalamus, and hypothalamus (15) and the "searching" response elicited from prefrontal cortex is abolished by thalamic and intracapsular lesions (164). Inhibition of the knee jerk in the cat follows stimulation of either corticifugal fibers traversing the caudate nucleus or stimulation of fibers arising in the basal ganglia and upper reticular formation (143). Adrenal medullary hormones may excite or inhibit cortically induced movements through actions in the diencephalon and reticular formation (280).

Further important descending diencephalic and reticular influences on motor activity are described. The cat's linguomandibular reflex is facilitated and inhibited from reticular zones which exercise generally converse effects on reflexes elsewhere (175). Stimulation of the amygdala elicits jaw and face movements after bilateral removal of cortical face representations (17). Shivering in cats is abolished by lesions in a fairly discrete extrapyramidal pathway running from posterior hypothalamus to spinal cord (29). The bulbar reticular formation inhibits spinal cord dorsum potentials and ventral root reflexes from cutaneous and muscle afferents (198). Human spasticity is reduced by chlorpromazine possibly by diminishing excessive reticular facilitatory influences (19). Mettler has emphasized the potentially variable pathophysiology to be found in diseases of the basal ganglia (212).

Much new light has been shed on the control exercised by the cerebellum in motor activity. A new concept of cerebellar functional organization has already been mentioned (55). Granit *et al.* have observed that excision of the anterior lobe of the cerebellum results in a paralysis of the gamma efferent mechanism, controlling the intrafusal muscle bundles (135). The gamma ventral horn cells are under the control of two pathways from the mesencephalic tegmentum, one rapidly conducting and crossed and the other slowly conducting and widely distributed over the cord (134). The

effects are reported of deafferentation and spinal transection on decerebrate rigidity in dogs with various chronic cerebellar lesions (287). The mechanisms of eye-centering and compulsive eye-opening involving cortical and subcortical structures have been discussed (22, 25). The role of Perlia's nucleus in convergence is challenged by Warwick (304) since its neurones are not internuncial but contribute to the oculomotor nerve.

Certain aspects of respiratory functions related to reticular mechanisms have been described (20, 100, 128, 314).

The Final Common Path

The processes of excitation and inhibition in spinal motoneurones continue to attract attention, although it may be fairly remarked that at least some of the towering edifices of hypothesis appear to go beyond the experimental evidence.

The beautiful microscopic studies of Young *et al.* reveal a thin membrane at the motoneurone surface to which are applied the terminal boutons, more numerous than hithero supposed. Neuronal respiratory exchanges appear to occur through the protoplasm of glial cells (313, 317).

Excitability of the motoneurone; the stretch reflex.—The chronaxie of toad spinal motoneurones as measured with intracellular electrodes is twenty times that of a myelinated axon (12). Facilitation and synchronization of motoneurone discharge follow constant subliminal depolarizing currents (33, 34). Granit concludes that tetanization or stretch create a long-lasting state of post-tetanic potentiation of ventral horn cells to subsequent stretch reflexes, and that in this way single ventral horn cells have been rendered spastic. The natural frequencies of large spindle endings excited by gamma efferents are high enough to set up this facilitation, and rebound to stretch may be one of its consequences (133). Ventral root discharges in the strychninized cord can be disturbed or reset by activation of polysynaptic reflex paths but not by monosynaptic reflexes (181).

Basic to the problem of the stretch reflex is the question of transmitter potentiality of the muscle afferent volley, concerned with its capacity to excite not only its own motoneurones (homonymous transmission) but also the motoneurones of synergic muscles (heteronymous transmission). In investigations by Lloyd & McIntyre (202, 203) and Hunt & Rall (159, 160, 260) attempts have been made to describe monosynaptic reflex behavior of a "synthetic" motoneurone pool in terms of the observed behavior in a number of individuals, and seeking a resemblance between the behavior of synthetic and "natural" pools. Since different motoneurones respond to homonymous and heteronymous volleys, there appear to be differences in presynaptic organization rather than differences in post-synaptic threshold. During the course of the ventral root potential, increased excitability of the ventral root is observed close to the cord (129).

Inhibitory processes in motoneurones.—Inhibition of motoneurone activity has been studied principally in relation to the effects of afferent volleys

from antagonist muscles, which have been considered to synapse either directly or through an intermediary neurone on the motoneurone surface. An additional inhibitory mechanism has been postulated involving recurrent axon collaterals of motoneurones which may synapse with interneurones (Renshaw cells) in the ventral horn and the Renshaw axons may in turn exert an inhibitory influence at the motoneurone surface.

The properties of the motoneurone membrane have been studied by Coombs, Eccles & Fatt (70 to 73). From the effects of injection of a wide variety of cations and anions directly into the interior of the cell, it is postulated that ionic pumps expending metabolic energy are involved in transporting potassium and sodium ions across the cell membrane, and that the inhibitor substance greatly increases the permeability to some ions, such as potassium and chloride. However, difficulties attach to the interpretation of the inhibitory post-synaptic potential recorded intracellularly as a hyperpolarization. Easton has pointed out that in muscle, at least, the distortion in intracellular records from activity in adjacent fibers can imitate the spikes recorded in the innervation field of the muscle after nerve stimulation and resemble the hyperpolarization in central nervous system neurones construed as reflecting inhibition (87).

Eccles, Fatt & Landgren have systematically explored the potential fields of inhibitory presynaptic terminals and suggest that even the simplest central inhibitory pathways appear to operate through a short-axon interneurone activated through collateral branches of primary afferent fibers (90). From both histological and physiological studies Sprague concludes, on the contrary, that at least a part of short latency inhibition initiated by dorsal root afferents is monosynaptic, and that whereas facilitation is associated with axosomatic and axodendritic terminals, inhibition may be associated with axodendritic terminals alone (285). A similar correlation of inhibitory afferent impulses with dendritic activation by afferents reaching the cell directly is reported by Edisen (91) and in the crayfish by Kuffler & Eyzaguirre (186).

The role of the Renshaw cells in a cholinergically operated inhibitory mechanism has been investigated by Eccles, Eccles & Fatt (89). They conclude that surrounding the blood vessels in the CNS there may be a diffusional barrier to prostigmine and *d*-tubocurarine and a further barrier greatly impedes the diffusion of acetylcholine from synaptic regions. However, Frank & Fuortes (108, 109) conclude from their studies that the destination and function of impulses generated by Renshaw cells can be presumed with only a smaller degree of probability, and emphasize that, as originally pointed out by Renshaw, while these cells may inhibit motoneurones, their functional role must await anatomical corroboration. Frank & Fuortes consider that the theories of Eccles *et al.* are compatible with their results only if it is assumed that short spikes are recorded solely from axons and that show potentials are not recorded from axons. They stress their findings that synchronous activity in neighboring units during antidromic stimulation can affect intracellular records.

Inhibition in the course of intermediary potentials evoked by afferent volleys has been studied by Austin & McCouch (16, 207) who conclude that inhibition in the course of ipsilateral flexor reflexes occurs largely in the dorsal horn, whether the source of the inhibition is ipsilateral or crossed. Ipsilateral inhibition of a crossed reflex occurs predominantly in the ventral horn.

Peripheral studies of integrated somatic motor patterns.—A number of human electromyographic studies have appeared concerning the role of the intercostal muscles (48), the erectores spinae (103) and the laryngeal muscles (98). Similar studies in animals have included the muscles of deglutition (86) and the middle ear (93). Body reflexes have been observed in intact and spinal man (161, 252). An interesting comparative study traces the increasing structural complexity of motor nerve endings in the vertebrate series (69).

Cerebral Associative Mechanisms, including some Cortico-subcortical Interrelations

The borderland between the easily discerned immediate effects of an afferent cortical sensory volley, and the much less tangible ensuring changes in the processes of perception are indeed fascinating frontiers in neurophysiological research (125). Perception may be regarded as a process demanding spontaneous action on the part of the perceiving individual, involving the isolation and subsquent intensification of one or more patterns of neural activity (261). The problem has been studied in relation to pain perception and sudomotor responses in individuals showing different levels of anxiety (248) and it is suggested that we distinguish pain at three levels of symbolization arranged in a hierarchy of increasing complexity (289).

On a broad comparative basis, the structural factor of cortical cell types has been further investigated (223). Certain differential effects of unilateral cerebral lesions are seen in subsequent learning of tactile pattern discrimination, spatial battery performance, and finger localization (23, 151, 262). A "time error" in weight judgment occurs after parietal lobe lesions, and is not specific for the affected hand (307). Apractognosia resulting from well-localized lesions in parieto-occipitotemporal cortex has been investigated by Hecaen *et al.* (150).

The role of corticifugal pathways in behavioral arousal and perception has been studied by Segundo, Arana & French. Arousal from normal sleep can be induced from restricted cortical zones which also yield alerting reactions with liminal stimulation in the waking state, whereas no responses ensue from powerful stimulation of other cortical regions (273). The active cortical regions (motor cortex, posterior cingulate region, superior temporal gyrus) resemble in distribution the restricted "epileptogenic" zones mapped by French, Gernandt & Livingston (111). Rossi & Brodal conclude that fibers to the pontine and medullary reticular formation arise from all parts of the cerebral cortex, but mainly from "motor" cortex, with substantial contributions from medial and basal surfaces, and that the majority terminate in two well-circumscribed areas (266). The electrophysiological corre-

lates of conditioned responses to clicks have been tested in records from the cochlear nucleus (115, 152). Mesencephalic reticular lesions abolish cortical seizures induced by metrazol (110).

Van Harreveld and his colleagues conclude that spreading cortical depression may curtail and perhaps prevent cortical convulsions in the rabbit. Spreading depression can be elicited in rabbits, cats, and monkeys in the absence of discernible cortical damage, and it is considered to be a phenomenon of normal cortex. The slow cortical potential wave does not appear to be its propagation mechanism (145, 146, 147); Grafstein (131) concludes that intense neuronal activity preceding depression may liberate potassium ions in sufficient quantity to spread depression.

EEG studies.—Only some of the investigations concerned with cortical associative mechanisms can be mentioned here. EEG changes in schizophrenics are consistent with diencephalic dysfunction (24, 31). Unilateral abolition of the alpha blocking responses is seen in cases of disturbed symbolic functions (aphasia, agnosia) with unilateral cerebral lesions (18). A wide variety of abnormalities are seen in temporal and frontal leads of children with psychomotor epilepsy (126). Apnea as a means of EEG activation has been tested (281).

The frontal lobes.—Further attempts to define area 4s in the monkey by strychnine neuronography have been unsuccessful (211), although a suppressor strip in the superior temporal gyrus has been reported (106). Clinical epilepsy follows application of alumina cream to the sensorimotor cortex whereas scarification is without effect (183). Motor defects from precentral ablations may not be due to acts lost through excision of the locus of a "habit", but rather should be considered as a "scotoma of action" (254).

The effects of lobotomy in the monkey appear within a few hours of operation and delayed effects cannot be detected (237). Bilateral removal of the prefontal area results in a rate of locomotion which is reliably higher, less variable, and less susceptible to decay than in normal monkeys or following bilateral removal of temporal neocortex (112). Results with a multiple choice maze test suggest that it is sensitive to damage localized to temporal or frontal lobes (94). Frontal lesions in the monkey interfere with ability to perform object alternation tasks (256) and impairment in delayed response problems is related to some aspect of "predelay" (220, 221).

In human studies, evoked electrical activity from the depths of the frontal lobe does not modify behavior or mobility in the absence of a generalized spread (82), and focal spike discharges are seen here in some chronically psychotic patients during hallucinated episodes (274, 275).

Visual and auditory associative functions.—Interocular transfer studies provide most interesting information on normal development patterns in the visual pathway, with evidence of a type of functional equivalence on the two sides of considerable complexity (229). In chimpanzees the overlap of optic fibers from the two retinae is initially incomplete and inadequate for interocular transfer (62). Monkeys fail to acquire discrimination in object-quality learning after a small vertical displacement of the stimulus-object (227). No

histological changes can be detected in any part of the visual system of monkeys kept in darkness, blue light, or red light (61). Repetitive stimulation of the optic nerve can block strychnine waves in the rabbit's visual area, and also in the strychninized masticatory area (14).

Lowered auditory flutter fusion thresholds follow widely scattered unilateral cortical lesions and are interpreted as a loss in differential sensitivity to the intensity of white noise (59). No permanent effects on conditioned responses to sound and tactile stimuli follow bilateral removal of the dog's auditory cortex (296). Increased adrenal weight follows repeated audiogenic seizures (4).

The limbic lobe.—It has become increasingly obvious that a knowledge of the interrelations between rhinencephalic structures and the central reticular areas of the brain stem would shed much light on the physiological mechanisms of emotional arousal (204, 251). There is additional evidence that the hippocampus may receive caudally directed fibers via the fornix and that these fibers arise in septal nuclei and from reticular areas of the thalamus (136, 209, 210). Such connections would provide pathways through which reticular mechanisms concerned in arousal would come to involve rhinencephalic structures. Bucy & Klüver have recently described a wide variety of subcortical connections of the temporal lobe (46). Subcortical secondary olfactory pathways in a reptile have been described with particular reference to the role of the stria medullaris bundle (116). This bundle also appears to form a major efferent pathway from the entorhinal area in the marsupial to central tegmental areas of the midbrain (2), thus suggesting that the rhinencephalon may involve the brainstem reticular systems at both diencephalic and midbrain levels through a re-entrant pathway. This is supported by the finding that these two regions of the brain stem are the principal zones eliciting affective responses (158).

Studies of neuronal activity in the hippocampus indicate its suceptibility to volatile anesthetics (76) and that individual units may respond to either specific types of afferent stimulation, or to many sensory modalities (137). Removal of the entorhinal area may abolish the capacity of the hippocampus to respond to alerting stimuli by a series of rhythmic slow waves (49, 50). The fastest travelling waves on the cortical surface are seen in the afterdischarges from hippocampal stimulation (244).

Recent studies emphasize the low threshold of hippocampal structures to seizure discharge and discuss the role of emotional and psychological factors in initiation of seizures (10, 196, 263). A high incidence of unstable behavior is reported in patients with and without a history of seizures who exhibit "temporal spikes" (95), and paroxysmal depressive reactions may occur in uncinate epilepsy (306). The production of experimental temporal lobe seizures with alumina cream is reported (316) and Maclean *et al.* conclude that reserpine may act on a system involving the hippocampus and hypothalamus, and that insulin convulsions depress subsequent hippocampal protein synthesis (205).

Behavior studies following a variety of subcortical and limbic resections

indicate possible anatomical interrelationships. Faster extinction of a conditioned emotional response follows habenular lesions than other subcortical resections (36). The alerting response to prefrontal cortical stimulation in the cat persists after destruction of habenulae, striae medullares, cingulum, and fornices (164). Destruction of the rat's median cerebral cortex has a profound effect on nest construction and maternal behavior (286). Bilateral removal of the temporal lobe in man has extreme effects on mental habitus (292). Kennard has studied the complex effects on the temporal lobe syndrome of additional frontal and cingulate lesions (169). Mishkin, Pribram and their colleagues have exhaustively examined the relative effects of visual discrimination of separate lesions involving the lateral aspect of the temporal lobe, the inferior surface including most of the hippocampal gyrus, and the hippocampal formation. They conclude that ventral resections produce markedly greater impairment of visual discrimination than does hippocampectomy or other temporal lesions. Modality-specific performance decrements follow circumscribed lesions of parietotemporopreoccipital cortex (217, 218, 219, 253, 255). Affective changes and somatic movements follow limbic stimulation (5).

A few of many hypothalamic studies related to emotional functions may be mentioned (64). The neural control of the hypophysis has been comprehensively reviewed by Harris (148). Emotional disturbance of milk-ejection results essentially from partial or complete inhibition of oxytocin release from the posterior pituitary (78, 79). Hypothalamic control of drinking, antidiuresis and milk-ejection in the goat has been tested (7, 8, 9). The development of temperature regulation in the first month of life and its hypothalamic control have been investigated (29, 167).

A number of studies in cybernetics have appeared (77, 104, 138, 239, 299).

Cerebral Blood Supply and Cerebrospinal Fluid Circulation

The tonus of extracranial arteries of the head may be significant in determining cerebral blood flow (44) and mechanisms of spinal blood flow have been examined (312). Methods are described for measurement of total and regional cerebral blood flow (163, 178). Meyer & Denny-Brown have investigated the effects of various injuries on cerebral circulation and conclude that brain trauma causes first a local transient paralysis of neurones complicated later by ischemia and metabolic disturbances (213, 214, 215). The ground substance of the central nervous system contributes to the blood-brain barrier and may be elaborated and maintained by neurones and neuroglia (153). The transfer of sodium and bromide ions between blood, cerebrospinal fluid, and brain tissue has been examined (236). Electroshock increases the permeability of the blood-brain barrier (3). Wolff & Tschirgi conclude that cerebrospinal fluid is incapable of transporting from the blood nutrient substrates essential in neural activity (310).

Cerebral Metabolism

Recent research in this field appears to point the way to a much broader understanding of the essential metabolic paths in central neurones (208). In a masterly review, Gerard has summarized recent developments (123). Stimulation of certain hypothalamic centers doubles cerebral oxygen consumption and these centers are highly resistant to low oxygen and carbohydrate and to high carbon dioxide concentrations. Phosphorylation is inhibited during excitation of frog nerve (1) and chlorpromazine inhibits phosphorylation specificially in thalamus and basal ganglia without similar cortical effects. No change in ATP synthesis occurs in cat cortex under barbiturate narcosis (139). Ling (199) suggests that energy is not required to maintain resting ionic composition of conductive tissue, but that ATP may be required to regulate the structural properties of protein chains presumably involved in the selective accumulation of intracellular potassium. The effects of potassium ions and diffusion of sodium ions have been investigated in cerebral tissue (99, 119).

A number of studies have been directed to the role of protein metabolism in neural activity (122). Radioactive tracer studies (114, 168, 205) indicate a considerably higher turn-over for brain proteins than did previous investigations which had neglected such factors as the blood-brain barrier. From observed interaction between reserpine, serotonin, and LSD in the brain, it is suggested that serotinin may be a neurohumoral agent (41, 249, 279).

The role of carbon dioxide as an anticonvulsant is discussed (222, 311) and its effects on the EEG (226) and on the duration of barbiturate narcosis are reviewed (173). In contrast to the findings in animals surviving an acute anoxic episode, local anoxia induced embolically causes a very rapid swelling of brain tissue, possibly due to intracellular fluid accumulation (92).

Further investigations of the significance of acetylcholine as a cerebral transmitter substance indicate that its synthesis in guinea pig brain slices is competitively inhibited by physostigmine and neostigmine (277). Atropine appears to act in the deeper cortical layers by blocking a presumably cholinergic tonic inhibitory system (60). Forced circling movements in rabbits following intra-arterial injection of diethylfluorophosphate suggest a cholinergic mechanism in the cerebral cortex and caudate nucleus (11). A barrier may greatly impede the diffusion of acetylcholine from synaptic regions (89). Cholinesterase is mainly concentrated in defined areas of the mesencephalic and isthmic regions of the frog's brain (278). An inhibitory factor has been isolated from the brain and spinal cord of mammals capable of rapid abolition of monosynaptic tendon reflexes and facilitation of polysynaptic reflexes (101, 102). Epileptiform discharges occur in brain and spinal cord in anaphylactic shock (38).

Endocrine factors may be of unsuspected importance in cerebral functions. Significant reduction in cerebral axon density is seen in hypoparathyroidism in rats (88). Complete replacement of alpha by generalized theta

rhythm is seen in post-partum hypopituitrism (157). Local application of hydrocortisone has no effect on the electrocorticogram (238).

Innovations in Physiological Techniques

Methods for the production of cerebral lesions with the aid of ultrasonics (113) and radioactive spheres (35) are described. An attempt has been made to develop functional brain mapping by utilizing the rate of incorporation of radioactively labelled materials by stimulated and nonstimulated CNS neurons (168). A silver staining technic is described for histological identification of microelectrode tracts (6).

Books, Monographs and Symposia

Much interesting material in this field has appeared in book form (37, 47, 127, 148, 208, 301, 309). A panel discussion on the central neurophysiology of psychosomatic phenomena has been published (125). The first comprehensive account of the electrical behavior of the olfactory epithelium appears as a monograph (240). A festschrift to mark the 25th anniversary of Dr. John Fulton's association with the laboratory of physiology at Yale University contains many worthy tributes to a leader in this field (156).

LITERATURE CITED

1. Abood, L. G., and Goldman, E., *Am. J. Physiol.*, **184,** 329–32 (1956)
2. Adey, W. R., *J. Anat. Soc. India*, **4,** 27–36 (1955)
3. Aird, R. B., Strait, L. A., Pace, J. W., Hrenoff, M. K., and Bowditch, S. C., *Arch. Neurol. Psychiat.*, **75,** 371–78 (1956)
4. Amour, F. E. d', and Shaklee, A. B., *Am. J. Physiol.*, **183,** 269–91 (1955)
5. Anand, B. K., and Dua, S., *Science*, **122,** 1139 (1955)
6. Andersen, P., *Acta Physiol. Scand.*, **35,** 305–11 (1956)
7. Andersson, B., and McCann, S. M., *Acta Physiol. Scand.*, **33,** 333–46 (1955)
8. Andersson, B., and McCann, S. M., *Acta Physiol. Scand.*, **35,** 191–201 (1955)
9. Andersson, B., and McCann, S. M., *Acta Physiol. Scand.*, **35,** 312–20 (1956)
10. Andy, O. J., and Akert, K., *J. Neuropathol. Exptl. Neurol.*, **14,** 198–213 (1955)
11. Aprison, M. H., Nathan, P., and Himwich, H. E., *Am. J. Physiol.*, **184,** 244–52 (1956)
12. Araki, T., and Otani, T., *J. Neurophysiol.*, **18,** 472–85 (1955)
13. Arden, G. B., and Tansley, K., *J. Physiol.*, **130,** 225–32 (1955)
14. Arduini, A., Magni, F., and Roger, A., *J. Physiol. (Paris)*, **47,** 849–56 (1955)
15. Auer, J., *J. Anat. (London)*, **90,** 30–41 (1956)
16. Austin, G. M., and McCouch, G. P., *J. Neurophysiol.*, **18,** 441–51 (1955)
17. Baldwin, M., Frost, L. L., and Wood, C. D., *Neurology*, **6,** 288–93 (1956)
18. Bancaud, J., Hecaen, A., and Lairy, G. C., *Electroencephalog. Clin. Neurophysiol.* **7,** 179–92 (1955)
19. Basmajian, J. V., and Szatmari, A., *Neurology*, **5,** 856–60 (1955)
20. Baxter, D. W., and Olszewski, J., *J. Neurophysiol.*, **18,** 276–87 (1955)
21. Beidler, L. M., Fishman, I. Y., and Hardiman, C. W., *Am. J. Physiol.*, **181,** 235–39 (1955)
22. Bender, M. B., *Arch. Neurol. Psychiat.*, **73,** 685–99 (1955)

23. Benton, A. L., *Arch. Neurol. Psychiat.*, **74**, 583–89 (1955)
24. Berard, E., and Lairy, G. C., *Electroencephalog. Clin. Neurophysiol.*, **7**, 545–52 (1955)
25. Berlin, L., *Arch. Neurol. Psychiat.*, **73**, 597–601 (1955)
26. Berry, C. M., Anderson, F. D., and Brooks, D. C., *J. Neurophysiol.*, **19**, 144–53 (1956)
27. Biagio, F. di, and Grundfest, H., *J. Neurophysiol.*, **19**, 10–20 (1956)
28. Biemond, A., *Arch. Neurol. Psychiat.*, **75**, 231–44 (1956)
29. Birzis, L., and Hemingway, A., *J. Neurophysiol.*, **19**, 37–43 (1956)
30. Bishop, G. H., and Clare, M. H., *J. Comp. Neurol.*, **103**, 269–304 (1955)
31. Blum, R. H., *J. Mental Sci.*, **102**, 160–67 (1956)
32. Boernstein, W. S., *Yale J. Biol. Med.*, **28**, 208–15 (1955–56)
33. Bonnet, V., *Arch. Intern. Physiol. Biochim.*, **64**, 141–67 (1956)
34. Bonnet, V., *Arch. Intern. Physiol. Biochim.*, **64**, 168–91 (1956)
35. Boyesen, S., and Campbell, J. B., *Yale J. Biol. Med.*, **28**, 216–24 (1955–56)
36. Brady, J. V., and Nauta, W. J. H., *J. Comp. Physiol. Psychol.*, **48**, 412–20 (1955)
37. Brain, R., and Strauss, E. B., *Recent Advances in Neurology and Neuropsychiatry* (J. & A. Churchill, London, England, 311 pp., 1955)
38. Brandon, A., *Electroencephalog. Clin. Neurophysiol.*, **7**, 371–74 (1955)
39. Brindley, G. S., *J. Physiol.*, **130**, 35–44 (1955)
40. Brodal, A., and Rossi, G. F., *Arch. Neurol. Psychiat.*, **74**, 68–87 (1955)
41. Brodie, B. B., Pletscher, A., and Shore, P. A., *Science*, **122**, 968 (1955)
42. Brooks, C. McC., and Koizumi, K., *J. Neurophysiol.*, **19**, 61–74 (1956)
43. Brown, G. L., and Holmes, O., *Proc. Roy. Soc.* (*London*), [B], **145**, 1–13 (1956)
44. Browne, K. M., Warner, W. A., and Walker, A. E., *J. Neurosurg.*, **12**, 634–42 (1955)
45. Bryant, S. H., and Tobias, J. M., *J. Cellular Comp. Physiol.*, **46**, 71–96 (1955)
46. Bucy, P. C., and Klüver, H., *J. Comp. Neurol.*, **103**, 151–252 (1955)
47. Cajal, S. R., *Studies on the Cerebral Cortex*, Translated by L. M. Kraft (Lloyd-Luke Medical Books, London, England, 179 pp., 1956)
48. Campbell, E. J. M., *J. Physiol.*, **129**, 12–26 (1955)
49. Carreras, M., Macchi, G., Angeleri, F., and Urbani, M., *Boll. soc. ital. biol. sper.*, **31**, 1–3 (1955)
50. Carreras, M., Macchi, G., Angeleri, F., and Urbani, M., *Boll. soc. ital. biol. sper.*, **31**, 4–7 (1955)
51. Cauna, N., *Anat. Record*, **124**, 77–94 (1956)
52. Causey, G., and Hoffmann, H., *Brain*, **78**, 661–68 (1955)
53. Causey, G., and Hoffmann, H., *J. Anat.* (*London*), **90**, 1–4 (1956)
54. Causey, G., and Stratmann, C. J., *Proc. Roy. Soc.* (*London*), [B], **144**, 520–27 (1956)
55. Chambers, W. W., and Sprague, J. M., *J. Comp. Neurol.*, **103**, 105–30 (1955)
56. Chambers, W. W., and Sprague, J. M., *Arch. Neurol. Psychiat.*, **74**, 653–80 (1955)
57. Chang, H. T., *J. Neurophysiol.*, **18**, 332–52 (1955)
58. Chang, H. T., *J. Neurophysiol.*, **18**, 452–71 (1955)
59. Chapman, L. F., Symmes, D. F., and Halstead, W. C., *J. Comp. Physiol. Psychol.*, **48**, 421–25 (1955)
60. Chatfield, P. O., and Lord, J. T., *Electroencephalog. Clin. Neurophysiol.*, **7**, 553–56 (1955)

61. Chow, K. L., *J. Comp. Neurol.*, **102,** 597–606 (1955)
62. Chow, K. L., and Nissen, H. W., *J. Comp. Physiol. Psychol.*, **48,** 229–37 (1955)
63. Clark, E. C., and Dodge, H. W., *Neurology*, **5,** 671–74 (1955)
64. Cleghorn, R. A., *Psychosomat. Med.*, **17,** 367–76 (1955)
65. Clerc, N. A., Turner, M., and Berard, E., *Electroencephalog. Clin. Neurophysiol.*, **8,** 35–39 (1956)
66. Cohen, L. A., *Yale J. Biol. Med.*, **28,** 225–32 (1955–56)
67. Cohen, L. A., and Cohen, M. L., *Am. J. Physiol.*, **184,** 433–37 (1956)
68. Cohen, M. J., Hagiwara, S., and Zotterman, Y., *Acta Physiol. Scand.*, **33,** 316–32 (1955)
69. Cole, W. V., *J. Comp. Neurol.*, **102,** 671–716 (1955)
70. Coombs, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.*, **130,** 291–325 (1955)
71. Coombs, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.*, **130,** 326–73 (1955)
72. Coombs, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.*, **130,** 374–95 (1955)
73. Coombs, J. S., Eccles, J. C., and Fatt, P., *J. Physiol.*, **130,** 396–413 (1955)
74. Cooper, S., Daniel, P. M., and Whitteridge, D., *Brain*, **78,** 564–83 (1955)
75. Cowan, W. M., and Powell, T. P. S., *J. Neurol. Neurosurg, Psychiat.*, **18,** 266–79 (1955)
76. Cragg, B. G., and Hamlyn, L. H., *J. Physiol.*, **129,** 608–27 (1955)
77. Cragg, B. G., and Temperley, H. V. N., *Brain*, **78,** 304–16 (1955)
78. Cross, B. A., *J. Endocrinol.*, **12,** 15–28 (1955)
79. Cross, B. A., *J. Endocrinol.*, **12,** 29–37 (1955)
80. Dawson, G. D., *J. Physiol.*, **131,** 436–51 (1956)
81. Dawson, I. M., Hossack, J., and Wyburn, G. M., *Proc. Roy. Soc.* (*London*), [B], **144,** 132–42 (1955)
82. Delgado, J. M. R., Hamlin, H., and Koskoff, Y. D., *Yale J. Biol. Med.*, **28,** 233–44 (1955–56)
83. Delgado, J. M. R., and Livingston, R. B., *Yale J. Biol. Med.*, **28,** 245–52 (1955–56)
84. Dorpat, T. L., and Holmes, T. H., *Arch. Neurol. Psychiat.*, **74,** 628–40 (1955)
85. Doust, J. W. L., and Coleman, L. I. M., *A.M.A. Arch. Neurol. Psychiat.*, **74,** 650–80 (1955)
86. Doty, R. W., and Bosma, J. F., *J. Neurophysiol.*, **19,** 44–60 (1956)
87. Easton, D. M., *J. Neurophysiol.*, **18,** 375–87 (1955)
88. Eayrs, J. T., *Acta Anat.*, **25,** 160–83 (1955)
89. Eccles, J. C., Eccles, R. M., and Fatt, P., *J. Physiol.*, **131,** 154–69 (1956)
90. Eccles, J. C., Fatt, P., and Landgren, S., *J. Neurophysiol.*, **19,** 75–98 (1956)
91. Edisen, A. E. U., *Am. J. Physiol.*, **184,** 223–32 (1956)
92. Edstrom, R. F. S., and Essex, H. E., *Neurology*, **6,** 118–24 (1956)
93. Eliasson, S., and Gisselsson, L., *Electroencephalog. Clin. Neurophysiol.*, **7,** 399–406 (1955)
94. Elithorn, A., *J. Neurol. Neurosurg. Psychiat.*, **18,** 287–92 (1955)
95. Ervin, F., Epstein, A. W., and King, H. E., *Arch. Neurol. Psychiat.*, **74,** 488–97 (1955)
96. Eyzaguirre, C., and Kuffler, S. W., *J. Gen. Physiol.*, **39,** 87–120 (1955)
97. Eyzaguirre, C., and Kuffler, S. W., *J. Gen. Physiol.*, **39,** 121–54 (1955)
98. Faarborg-Andersen, K., and Buchthal, F., *Nature*, **177,** 340–41 (1956)
99. Fain, P., Dennis, J., and Harbough, F. G., *Am. J. Physiol.*, **182,** 415–18 (1955)
100. Fischgold, H., and Arfel-Capdevielle, M., *Electroencephalog. Clin. Neurophysiol.*, **7,** 165–78 (1955)

101. Florey, E., and McLennan, H., *J. Physiol.*, **129,** 384–92 (1955)
102. Florey, E., and McLennan, H., *J. Physiol.*, **130,** 446–55 (1955)
103. Floyd, W. F., and Silver, P. H. S., *J. Physiol.*, **129,** 184–203 (1955)
104. Foerster, H. von, Mead, M., and Teuber, H. L., Editors, *Cybernetics, Circular Causal and Feedback Mechanisms in Biological and Social Systems* (The Macy Foundation, Trans. of the Tenth Congress, Corlies, Macy, New York, 100 pp., 1955)
105. Foltz, E. L., and Schmidt, R. P., *J. Neurosurg.*, **13,** 145–54 (1956)
106. Forster, F. M., and Huertas, J., *Yale J. Biol. Med.*, **28,** 265–72 (1955–56)
107. Francis, C. M., *J. Comp. Neurol.*, **103,** 355–83 (1955)
108. Frank, K., and Fuortes, M. G. F., *J. Physiol.*, **130,** 625–54 (1955)
109. Frank, K., and Fuortes, M. G. F., *J. Physiol.*, **131,** 424–35 (1956)
110. Freedman, D. A., and Ferriss, G. S., *Neurology* **6,** 173–78 (1956)
111. French, J. D., Gernandt, B. E., and Livingston, R. B., *Arch. Neurol. Psychiat.*, **75,** 260–74 (1956)
112. French, G. M., and Harlow, H., *J. Comp. Physiol. Psychol.*, **48,** 496–501 (1955)
113. Fry, W. J., Barnard, J. W., Fry, F. J., Krumins, R. F., and Brennan, J. F., *Science*, **122,** 517–18 (1955)
114. Gaitonde, M. K., and Richter, D., *Proc. Roy. Soc.* (*London*), [B], **145,** 83–99 (1956)
115. Galambos, R., Sheatz, G., and Vernier, G., *Science*, **123,** 376–77 (1956)
116. Gamble, H. J., *J. Anat.* (*London*), **90,** 15–29 (1956)
117. Gardner, E., Thomas, L. M., and Morin, F., *Am. J. Physiol.*, **183,** 433–37 (1955)
118. Gardner, W. J., Karnosh, L. J., McClure, C. C., and Gardner, A., *Brain*, **78,** 487–502 (1956)
119. Garoutte, B., and Aird, R. B., *Science*, **122,** 333–34 (1955)
120. Gasser, H. S., *J. Gen. Physiol.*, **38,** 709–28 (1955)
121. Gasser, H. S., *J. Gen. Physiol.*, **39,** 473–96 (1956)
122. Geiger, A., Yamasaki, S., and Lyons, R., *Am. J. Physiol.*, **184,** 239–43 (1956)
123. Gerard, R. W., *Am. J. Psychiat.*, **112,** 81–90 (1955)
124. Gernandt, B. E., and Terzuolo, C. A., *Am. J. Physiol.*, **183,** 1–8 (1955)
125. Glaser, G. H., *Psychosomat. Med.*, **17,** 337–46 (1955)
126. Glaser, G. H., and Golub, L. M., *Electroencephalog. Clin. Neurophysiol.*, **7,** 329–40 (1955)
127. Glees, P., *Neuroglia: Morphology and Function* (Basil Blackwell, and Mott, Oxford, England, 111 pp., 1955)
128. Goldensohn, E. S., *Psychosomat. Med.*, **17,** 377–82 (1955)
129. Goto, T., *Japan. J. Physiol.*, **6,** 40–46 (1956)
130. Graf, W., and Hjelmquist, U., *J. Comp. Neurol.*, **103,** 345–54 (1955)
131. Grafstein, B., *J. Neurophysiol.*, **19,** 154–71 (1956)
132. Granit, R., *J. Neurophysiol.*, **18,** 388–411 (1955)
133. Granit, R., *J. Physiol.*, **131,** 32–51 (1956)
134. Granit, R., and Holmgren, B., *Acta Physiol. Scand.*, **35,** 93–108 (1955)
135. Granit, R., Holmgren, B., and Merton, P. A., *J. Physiol.*, **130,** 213–24 (1955)
136. Green, J. D., and Adey, W. R., *Electroencephalog. Clin. Neurophysiol.*, **8,** 245–62 (1956)
137. Green, J. D., and Machne, X., *Am. J. Physiol.*, **181,** 219–24 (1955)
138. Gregory, R. L., and Cane, V., *Nature*, **176,** 1272 (1955)
139. Grenell, R. G., Mendelson, J., and McElroy, W. D., *J. Cellular Comp. Physiol.*, **46,** 143–61 (1955)

140. Grey Walter, W., *Nature*, **177**, 710 (1956)
141. Grossman, C., *Arch. Neurol. Psychiat.*, **74**, 186–202 (1955)
142. Gualtierotti, T., and Margaria, R., *Yale J. Biol. Med.*, **28**, 298–307 (1955–56)
143. Hankinson, J., Namin, P., and Ochs, S., *Brain*, **78**, 133–47 (1955)
144. Harpman, J. A., and Whitehead, T. P., *Brain*, **78**, 634–60 (1955)
145. Harreveld, A. van, and Stamm, J. S., *Electroencephalog. Clin. Neurophysiol.*, **7**, 363–70 (1955)
146. Harreveld, A. van, Stamm, J. S., and Christensen, E., *Am. J. Physiol.*, **184**, 312–20 (1956)
147. Harreveld, A. van, Terres, G., and Dernburg, E. A., *Am. J. Physiol.*, **184**, 223–38 (1956)
148. Harris, G. W., *Neural Control of the Pituitary Gland* (Edward Arnold and Co., London, England, 298 pp., 1955)
149. Heath, R. G., *Psychosomat. Med.*, **17**, 383–95 (1955)
150. Hecaen, H., Penfield, W., Bertrand, C., and Malmo, R., *Arch. Neurol. Psychiat.*, **75**, 400–34 (1956)
151. Heilbrun, A. B., *J. Comp. Physiol. Psychol.*, **49**, 10–14 (1956)
152. Hernandez-Peon, R., Scherrer, H., and Jouvet, M., *Science*, **123**, 331–32 (1956)
153. Hess, A., *Arch. Neurol. Psychiat.*, **74**, 149–57 (1955)
154. Hess, A., *Proc. Roy. Soc.* (*London*), [B], **144**, 496–506 (1956)
155. Himwich, H. E., and Rinaldi, F., *Yale J. Biol. Med.*, **28**, 308–19 (1955–56)
156. Hoff, H. E., *Yale J. Biol. Med.*, **28**, 165–67 (1955–56)
157. Hughes, R. R., and Summers, V. K., *Electroencephalog. Clin. Neurophysiol.*, **8**, 87–96 (1956)
158. Hunsperger, R. W., *Helv. Physiol. et Pharmacol. Acta*, **14**, 70–92 (1956)
159. Hunt, C. C., *J. Gen. Physiol.*, **38**, 801–11 (1955)
160. Hunt, C. C., *J. Gen. Physiol.*, **38**, 813–52 (1955)
161. Ikai, M., *Japan. J. Physiol.*, **6**, 29–39 (1956)
162. Ingvar, D. H., *Acta Physiol. Scand.*, **33**, 137–50 (1955)
163. Ingvar, D. H., and Söderberg, U., *Nature*, **177**, 339–40 (1956)
164. Jansen, J., Andersen, P., and Kaada, B. R., *Yale J. Biol. Med.*, **28**, 331–41 (1955–56)
165. Jansen, J., and Brodal, A., *Avhand. Norske, Videnskaps-Akad. Oslo*, **3**, 3–50 (1942)
166. Jefferson, G., *Brit. Med. J.*, **1**, 1405–8 (1955)
167. Jensen, C., and Ederstrom, H. E., *Am. J. Physiol.*, **183**, 340–44 (1955)
168. John, E. R., *J. Neuropathol. Exptl. Neurol.*, **15**, 103–16 (1956)
169. Kennard, M. A., *Yale J. Biol. Med.*, **28**, 342–50 (1955–56)
170. Kerr, D. I. B., and Hagbarth, K. E., *J. Neurophysiol.*, **18**, 362–74 (1955)
171. Kerr, D. I. B., Haugen, F. P., and Melzack, R., *Am. J. Physiol.*, **183**, 253–58 (1955)
172. Kessler, M. M., *Yale J. Biol. Med.*, **28**, 351–62 (1955–56)
173. Killion, P. J., and Schaeffer, K. E., *Am. J. Physiol.*, **183**, 44–45 (1955)
174. Kimura, R., Schuknecht, H. F., and Sutton, S., *J. Comp. Physiol. Psychol.*, **49**, 96–104 (1956)
175. King, E. E., Minz, B., and Unna, K. R., *J. Comp. Neurol.*, **102**, 565–96 (1955)
176. King, R. B., and Meagher, J. N., *J. Neurosurg.*, **12**, 393–402 (1955)
177. King, R. B., Meagher, J. N., and Barnett, J. C., *J. Neurosurg.*, **13**, 176–83 (1956)

178. Knapp, F. M., Hyman, C., and Bercel, N. A., *Yale J. Biol. Med.*, **28**, 363–71 (1955–56)
179. Köhler, W., Neff, W. D., and Wegener, J., *J. Cellular Comp. Physiol.*, **45**, Suppl. 1, 1–24 (1955)
180. Köhler, W., and Wegener, J., *J. Cellular Comp. Physiol.*, **45**, Suppl. 1, 25–54 (1955)
181. Koizumi, K., *Am. J. Physiol.*, **183**, 35–43 (1955)
182. Koketsu, K., *Am. J. Physiol.*, **184**, 338–44 (1956)
183. Kopeloff, L. M., Chusid, J. G., and Kopeloff, N., *Arch. Neurol. Psychiat.*, **74**, 523–26 (1955)
184. Krieger, H. P., and Bender, M. B., *Electroencephalog. Clin. Neurophysiol.*, **8**, 97–106 (1956)
185. Krieger, H., and Grundfest, H., *J. Neurophysiol.*, **19**, 3–9 (1956)
186. Kuffler, S. W., and Eyzaguirre, C., *J. Gen. Physiol.*, **39**, 154–84 (1955)
187. Laporte, Y., and Lundberg, A., *Acta Physiol. Scand.*, **36**, 204–18 (1956)
188. Laporte, Y., Lundberg, A., and Oscarsson, O., *Acta Physiol. Scand.*, **36**, 175–87 (1956)
189. Laporte, Y., Lundberg, A., and Oscarsson, O., *Acta Physiol. Scand.*, **36**, 188–203 (1956)
190. Lele, P. P., and Sinclair, D. C., *J. Neurol. Neurosurg. Psychiat.*, **18**, 120–24 (1955)
191. Lennox, M. A., and Madsen, A., *J. Neurophysiol.*, **18**, 412–24 (1955)
192. Lewis, P. R., *J. Physiol.*, **130**, 45–52 (1955)
193. Li, C.-L., *J. Physiol.*, **131**, 115–24 (1956)
194. Li, C.-L., Cullen, C., and Jasper, H. H., *J. Neurophysiol.*, **19**, 111–30 (1956)
195. Li, C.-L., Cullen, C., and Jasper, H. H., *J. Neurophysiol.*, **19**, 131–43 (1956)
196. Liberson, W. T., *Am. J. Psychiat.*, **112**, 91–106 (1955)
197. Liljestrand, G., and Zotterman, Y., *Acta Physiol. Scand.*, **35**, 380–89 (1956)
198. Lindblom, U. F., and Ottoson, J. O., *Acta Physiol. Scand.*, **35**, 203–14 (1956)
199. Ling, G., *Am. J. Phys. Med.*, **34**, 89–101 (1955)
200. Liu, C.-N., *Arch. Neurol. Psychiat.*, **75**, 67–77 (1956)
201. Livingston, R. B., *Psychosomat. Med.*, **17**, 347–54 (1955)
202. Lloyd, D. P. C., and McIntyre, A. K., *J. Gen. Physiol.*, **38**, 771–88 (1955)
203. Lloyd, D. P. C., and McIntyre, A. K., *J. Gen. Physiol.*, **38**, 789–99 (1955)
204. Maclean, P. D., *Psychosomat. Med.*, **17**, 355–66 (1955)
205. Maclean, P. D., Flanigan, S., Flynn, J. P., Kim, C., and Stevens, J. R., *Yale J. Biol. Med.*, **28**, 380–95 (1955–56)
206. Malis, L. I., and Kruger, L., *J. Neurophysiol.*, **19**, 172–86 (1956)
207. McCouch, G. P., and Austin, G. M., *Yale J. Biol. Med.*, **28**, 372–79 (1955–56)
208. McIlwain, H., *Biochemistry and the Central Nervous System* (J. & A. Churchill, Ltd., London, England, 272 pp., 1955)
209. McLardy, T., *J. Comp. Neurol.*, **103**, 305–26 (1955)
210. McLardy, T., *J. Comp. Neurol.*, **103**, 327–44 (1955)
211. Mendelow, H., and Wright, M. K., *Brain*, **78**, 433–40 (1955)
212. Mettler, F. A., *J. Neuropathol. Exptl. Neurol.*, **14**, 115–41 (1955)
213. Meyer, J. S., *Electroencephalog Clin. Neurophysiol.*, **8**, 107–16 (1956)
214. Meyer, J. S., and Denny-Brown, D., *Electroencephalog. Clin. Neurophysiol.*, **7**, 511–28 (1955)

215. Meyer, J. S., and Denny-Brown, D., *Electroencephalog. Clin. Neurophysiol.*, **7**, 528–44 (1955)
216. Mihailovic, L., and Delgado, J. M. R., *J. Neurophysiol.*, **19**, 21–36 (1956)
217. Mishkin, M., *J. Comp. Physiol. Psychol.*, **47**, 187–93 (1954)
218. Mishkin, M., and Hall, M., *J. Comp. Physiol. Psychol.*, **48**, 97–101 (1955)
219. Mishkin, M., and Pribram, K. H., *J. Comp. Physiol. Psychol.*, **47**, 14–20 (1954)
220. Mishkin, M., and Pribram, K. H., *J. Comp. Physiol. Psychol.*, **48**, 492–95 (1955)
221. Mishkin, M., and Pribram, K. H., *J. Comp. Physiol. Psychol.*, **49**, 36–40 (1956)
222. Mitchell, W. G., and Grubbs, R. C., *Science*, **123**, 223–24 (1956)
223. Mitra, N. L., *J. Anat. (London)*, **89**, 467–83 (1955)
224. Moncrieff, R. W., *J. Physiol.*, **130**, 543–58 (1955)
225. Morin, F., *Am. J. Physiol.*, **183**, 245–52 (1955)
226. Morrice, J. K. W., *Electroencephalog. Clin. Neurophysiol.*, **8**, 49–72 (1956)
227. Murphy, J. V., and Miller, R. E., *J. Comp. Physiol. Psychol.*, **48**, 221–24 (1955)
228. Murray, R. W., *Nature*, **176**, 698–99 (1955)
229. Myers, R. E., *J. Comp. Physiol. Psychol.*, **48**, 470–73 (1955)
230. Nakao, H., and Koella, W. P., *J. Neurophysiol.*, **19**, 187–95 (1956)
231. Nashold, B. S., Hanbery, J., and Olszewski, J., *Electroencephalog. Clin. Neurophysiol.*, **7**, 609–20 (1955)
232. Nathan, P. W., and Smith, M. C., *Brain*, **78**, 248–303 (1955)
233. Nathan, P. W., and Smith, M. C., *J. Neurol. Neurosurg. Psychiat.*, **18**, 181–90 (1955)
234. Nathan, P. W., and Smith, M. C., *J. Neurol. Neurosurg. Psychiat.*, **18**, 250–59 (1955)
235. Ochs, S., *Am. J. Physiol.*, **182**, 411–14 (1955)
236. Olsen, N. S., and Rudolph, G. G., *Am. J. Physiol.*, **183**, 427–32 (1956)
237. Orbach, J., *J. Comp. Physiol. Psychol.*, **49**, 46–51 (1956)
238. Ortiz-Galvan, A., and Morrell, F., *Arch. Neurol. Psychiat.*, **75**, 245–50 (1956)
239. Ostow, M., *Psychosomat. Med.*, **17**, 396–406 (1955)
240. Ottoson, D., *Acta Physiol. Scand.*, **35**, Suppl. 122, 1–83 (1956)
241. Papez, J. W., *Electroencephalog. Clin. Neurophysiol.*, **8**, 117–28 (1956)
242. Penfield, W., and Faulk, M. E., *Brain*, **78**, 445–70 (1955)
243. Perl, E. R., and Whitlock, D. G., *J. Neurophysiol.*, **18**, 486–501 (1955)
244. Petsche, H., Marko, A., and Monnier, M., *Helv. Physiol. Pharmacol. Acta*, **13**, 354–71 (1955)
245. Pfaffmann, C., *J. Neurophysiol.*, **18**, 429–440 (1955)
246. Phillips, C. G., *Quart. J. Exptl. Physiol.*, **41**, 58–69 (1956)
247. Phillips, C. G., *Quart. J. Exptl. Physiol.*, **41**, 70–84 (1956)
248. Piercy, M., Elithorn, I., Pratt, R. T. C., and Crosskey, M., *J. Neurol. Neurosurg. Psychiat.*, **18**, 155–62 (1955)
249. Pletscher, A., Shore, P. A., and Brodie, B. B., *Science*, **122**, 374–75 (1955)
250. Poggio, G. F., and Walker, A. E., *Yale J. Biol. Med.*, **28**, 419–27 (1955–56)
251. Poggio, G. F., Walker, A. E., and Andy, O. J., *Arch. Neurol. Psychiat.*, **75**, 350–61 (1956)
252. Pollock, L. J., Boshes, B., Zivin, I., Pyzik, S. W., Finkle, J. R., Tigay, E. L., Kesert, B. H., Arieff, A. J., Finkelman, I., Brown, M., and Dobin, N. B., *Arch. Neurol. Psychiat.*, **74**, 527–33 (1955)
253. Pribram, H. B., and Barry, J., *J. Neurophysiol.* **19**, 99–106 (1956)
254. Pribram, K. H., Kruger, L., Robinson, F., and Berman, A. J., *Yale J. Biol. Med.*, **28**, 428–43 (1955–56)

255. Pribram, K. H., and Mishkin, M., *J. Comp. Physiol. Psychol.*, **48**, 198–202 (1955)
256. Pribram, K. H., and Mishkin, M., *J. Comp. Physiol. Psychol.*, **49**, 41–45 (1956)
257. Purpura, D. P., *Arch. Neurol. Psychiat.*, **75**, 122–43 (1956)
258. Purpura, D. P., *J. Neurophysiol.*, **18**, 246–260 (1955)
259. Quilliam, T. A., and Sato, M., *J. Physiol.*, **129**, 167–76 (1955)
260. Rall, W., and Hunt, C. C., *J. Gen. Physiol.*, **39**, 397–422 (1956)
261. Reinhold, M., *Brain*, **78**, 417–32 (1955)
262. Reitan, R. M., *J. Comp. Physiol. Psychol.*, **48**, 474–477 (1955)
263. Rodin, E. A., Mulder, D. W., Faucett, R. L., and Bickford, R. G., *Arch. Neurol. Psychiat.*, **74**, 365–74 (1955)
264. Roger, A., Rossi, G. F., and Zirondoli, A., *Electroencephalog. Clin. Neurophysiol.*, **8**, 1–13 (1956)
265. Rosenzweig, M. R., and Wyers, E. J., *J. Comp. Physiol. Psychol.*, **48**, 426–31 (1955)
266. Rossi, G. F., and Brodal, A., *J. Anat. (London)*, **90**, 42–62 (1956)
267. Rossi, G. F., and Zirondoli, A., *Electroencephalog. Clin. Neurophysiol.*, **7**, 383–90 (1955)
268. Rovetta, P., *Electroencephalog. Clin. Neurophysiol.*, **8**, 15–24 (1956)
269. Russell, W. R., and Whitty, C. W. M., *J. Neurol. Neurosurg. Psychiat.*, **18**, 79–96 (1955)
270. Scheibel, M., Scheibel, A., Mollica, A., and Moruzzi, G., *J. Neurophysiol.*, **18**, 309–31 (1955)
271. Schiller, F., *Arch. Neurol. Psychiat.*, **75**, 203–19 (1956)
272. Scott, D., and Clemente, C. D., *J. Comp. Neurol.*, **102**, 633–70 (1955)
273. Segundo, J. P., Arana, R., and French, J. D., *J. Neurosurg.*, **12**, 601–13 (1955)
274. Sem-Jacobsen, C. W., Petersen, M. C., Lazarte, J. A., Dodge, H. W., and Holman, C. B., *Am. J. Psychiat.*, **112**, 278–88 (1955)
275. Sem-Jacobsen, C. W., Petersen, M. C., Lazarte, J. A., Dodge, H. W., and Holman, C. B., *Electroencephalog. Clin. Neurophysiol.*, **7**, 193–210 (1955)
276. Shaw, S. N., and Tobias, J. M., *J. Cellular Comp. Physiol.*, **46**, 53–70 (1955)
277. Shelley, H., *J. Physiol.*, **131**, 329–40 (1956)
278. Shen, S. C., Greenfield, P., and Boell, E. J., *J. Comp. Neurol.*, **102**, 717–44 (1955)
279. Shore, P. A., Silver, S. L., and Brodie, B. B., *Science*, **122**, 284–85 (1955)
280. Sigg, E., Ochs, S., and Gerard, R. W., *Am. J. Physiol.*, **183**, 419–26 (1955)
281. Silverman, D., *Electroencephalog. Clin. Neurophysiol.*, **8**, 41–48 (1956)
282. Sinclair, D. C., *Brain*, **78**, 584–614 (1955)
283. Sperry, R. W., and Miner, N., *J. Comp. Physiol. Psychol.*, **48**, 463–69 (1955)
284. Spiegel, E. A., and Szekely, E. G., *Electroencephalog. Clin. Neurophysiol.*, **7**, 375–81 (1955)
285. Sprague, J. M., *Proc. Anat. Soc. Great Britain and Ireland*, p. 13 (April, 1956)
286. Stamm, J. S., *J. Comp. Physiol. Psychol.*, **48**, 347–56 (1955)
287. Stella, G., Zatti, P., and Sperti, L., *Am. J. Physiol.*, **181**, 230–34 (1955)
288. Strange, P. H., *J. Physiol.*, **129**, 225–36 (1955)
289. Szasz, T. S., *Arch. Neurol. Psychiat.*, **74**, 174–81 (1955)
290. Szentagothai, J., and Albert, A., *Acta, Morphol. Acad. Sci. Hung.*, **5**, 43–51 (1955)
291. Tasaki, I., *J. Gen. Physiol.*, **39**, 377–96 (1956)
292 Terzian, H., and Ore, G. D., *Neurology*, **5**, 373–80 (1955)
293. Thomas, P. K., *J. Anat. (London)*, **90**, 5–14 (1956)

294. Travis, A. M., *Brain*, **78**, 155–73 (1955)
295. Travis, A. M., *Brain*, **78**, 174–98 (1955)
296. Tunturi, A. R., *Am. J. Physiol.*, **181**, 225–29 (1955)
297. Tunturi, A. R., *Am. J. Physiol.*, **184**, 321–28 (1956)
298. Turner, M., Berard, E., Turner, N., and Franco, N., *Electroencephalog. Clin. Neurophysiol.*, **8**, 25–34 (1956)
299. Uttley, A. M., *Proc. Roy. Soc.* (*London*), [B] **144**, 229–40 (1955)
300. Vastola, E. F., *Electroencephalog. Clin. Neurophysiol.*, **7**, 557–68 (1955)
301. Veith, I., Editor, *Perspectives in Physiology, An International Symposium* (American Physiological Society, Washington, D. C., 171 pp., 1954)
302. Verzeano, M., Naquet, R., and King, E. E., *J. Neurophysiol.*, **18**, 502–12 (1955)
303. Wall, P. D., McCulloch, W. S., Lettvin, J. Y., and Pitts, W. H., *Yale J. Biol. Med.*, **28**, 457–64 (1955–56)
304. Warwick, R., *Brain*, **78**, 92–114 (1955)
305. Watson, C. W., and Denny-Brown, D., *Electroencephalog. Clin. Neurophysiol.*, **7**, 341–56 (1955)
306. Weil, A. A., *J. Nervous Mental Disease*, **121**, 505–10 (1955)
307. Weinstein, S., *J. Comp. Physiol. Psychol.*, **48**, 203–07 (1955)
308. Whitteridge, D., *Quart. J. Exptl. Physiol.*, **40**, 331–36 (1955)
309. Windle, W. F., Editor, *Regeneration in the Central Nervous System* (Charles C Thomas, Springfield, Ill., 311 pp., 1955)
310. Wolff, P. H., and Tschirgi, R. D., *Am. J. Physiol.*, **184**, 220–22 (1956)
311. Woodbury, D. M., Rollins, L. T., Henrie, J. R., Jones, J. C., and Sato, T., *Am. J. Physiol.*, **184**, 202–08 (1956)
312. Woollam, D. H. M., and Millen, J. W., *J. Neurol. Neurosurg. Psychiat.*, **18**, 97–102 (1955)
313. Wyckoff, R. W. G., and Young, J. Z., *Proc. Roy. Soc.* (*London*), [B] **144**, 440–49 (1956)
314. Wyss, O. A. M., *Yale J. Biol. Med.*, **28**, 471–80 (1955–56)
315. Yamamoto, S., Sugihara, S., and Kuru, M., *Japan J. Physiol.*, **6**, 68–85 (1956)
316. Youmans, J. R., *Neurology*, **6**, 179–86 (1956)
317. Young, J. Z., *Endeavour*, **15**, 5–19 (1956)

KIDNEY[1]

By Stanley E. Bradley

Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York City, New York

As usual, the past year has witnessed the appearance of a number of monographs and reviews (1 to 5) dealing with special aspects of renal physiology as well as texts having a more general purview (6 to 8). The general orientation of *The Body Fluids, Basic Physiology and Practical Therapeutics* by Elkinton & Danowski (6) results in a tendency to deal somewhat superficially with renal and hemodynamic mechanisms and to stress methodology and the problem of fluid distribution in the body. A shorter and less inclusive survey of the same subject has been written by Welt (7). Homer Smith's latest opus, *Principles of Renal Physiology* (8), is an up-to-date account of the author's views in succinct and compact form.

STRUCTURAL BASIS OF RENAL PHYSIOLOGY

Important advances in the knowledge of the finer structure of the kidney resulting from improved methods of electron microscopy have given new impetus to attempts to correlate structure and function. This new evidence gives support to the view that glomeruli act as simple physical filters. The filtering surface of the glomerular capillaries is apparently composed of three separate layers. Endothelial cells cover the internal surface with a thin porous cytoplasmic lining [Pease (9, 10, 11), Piel *et al.* (12)]. Epithelial cells are attached to the external surface by "pedicels" at the ends of processes that lift the nucleus and the body of the cell away from the surface. Between pedicels and endothelial plate lies a homogeneous and continuous "basement membrane" (0.1 μ thick) with its inner and outer "cement layers." This must be presumed to be the sole filtering partition between blood and glomerular filtrate. The peritubular capillaries are lined by a similar fenestrated endothelium. Bowman's capsule appears to be laminated and thinly lined with flat epithelial cells (12).

Finger-like outgrowths (1.4 μ in length) projecting stiffly into the lumen make up the brush border of the proximal tubule. Occasional saccular invaginations seem to invade the substance of the cells at the base of brush border processes, coming into suggestive proximity to round or oval vacuoles. Thicker outgrowths pass from the central portion of the cell to the base. So tightly packed are these digital projections that the cell body appears to be compartmentalized by intracellular cell membranes. Mitochondria fill

[1] The survey of literature pertaining to this review was completed June, 1956. Owing to lack of space the Editors have omitted sections dealing with the renal excretion of organic compounds, including urea, uric acid, PAH and related compounds, amino acids and glucose, and the developmental and comparative physiology of the kidney.

each extension in a palisade arrangement giving rise to the "basal striations" disclosed by light microscopy. The compartments may also be interpreted as infoldings of the cell membrane and Pease (11) notes that this feature is even more marked and complex in the thin and distal tubular segments where basal alignment of the mitochondria does not occur. The mitochondria appear to be saccular and partitioned by transverse parallel plates. Mitochondria, nucleus, larger granules, vacuoles, and cell wall are bounded by "double-lined" membranes, whereas the so-called "microbodies" (about 0.3 $\mu \times 0.1$ μ) are enclosed in a single membrane. Pease (11) refers to the microbodies as "RNH granules" and believes they appear in the "microsomal fraction." The basement membrane appears to be the major continuously intact barrier between the blood and the tubular cells. Thus, a very large surface is afforded by the tubular cellular processes, cell-wall infoldings, intracellular organelles and "slotted," "fenestrated," or "trabeculated" plates of endothelial and epithelial capillary cells.

One of the most serious difficulties in interpreting renal function in terms of the electron-micrograph lies in the size of the tissue fragment which is examined. The same criticism may be leveled at data obtained in the study of individual nephrons obtained by microdissection. Nonetheless, this is the only means now at hand by which the local effects of disease on the nephron may be detected. Darmady & Stranack's (13) study of the nephron pathology in Fanconi's syndrome is a step in this direction. Even renal biopsy, which provides a large piece of tissue for examination, does not yield a reliable correlation between function and microanatomy (14, 15). The danger of bleeding appears to be reduced by the technique recommended by Muehrcke *et al.* (16), who believe that use of the Franklin cutting prongs reduces trauma. Other authors (14, 17) appear to be content with aspiration biopsy. In experienced hands renal tissue is obtained in 80 to 96 per cent of attempts.

THE RENAL CIRCULATION

The development of new methods and new conceptual approaches has resulted not only in a better understanding of the physiology of the renal circulation but also in a more lively appreciation of the uncertainties in current knowledge.

Methodology

By and large, the use of the clearance technique [employing Diodrast or sodium *p*-aminohippurate (PAH)] has proved a satisfactory and valid means of measuring renal blood flow without recourse to surgery or anesthesia. Diodrast enters the red cells in both dog and man; PAH, the red cells in the dog. Nedeljković (18, 19) has confirmed earlier work indicating that PAH enters the red cells more readily in venous blood, accounting in part for the discrepancies he finds between changes in blood flow measured directly and by the PAH clearance-and-extraction technique in kidneys

transplanted to the neck in dogs and perfused at various pressures by a pump. The extractions of PAH were very low in all four studies reported and analytical error may have contributed to the results. The delay in equilibrium between urine and plasma may also have been a source of error (18, 19) and possibly intracellular "storage" (19, 20) as well as the "dead-space time." Whatever its nature, "delay" imposes a limit upon the confidence with which change in flow may be followed by the clearance method. Estimation of flow on the basis of the disappearance of PAH from the blood following a single intravenous injection of a known amount has proved unreliable owing to the effect of movement of PAH from the blood into and out of "compartments" other than the urine. Sapirstein and his associates (21, 22) have brought forward a new formulation based on the simplifying assumption of a two-compartment distribution of PAH. They claim good agreement with "infusion clearances for PAH," but it should be noted that the "infusion clearance" alluded to involves indirect estimation of urinary excretion from the rate of infusion at equilibrium. Since this method is subject to some of the errors that may affect PAH disappearance, the "agreement" observed may be misleading. The uptake of nitrous oxide or radioactive krypton (Kr^{85}) by the kidney during equilibration following inhalation of the gas may be used in the estimation of the relative flow in spite of anuria or marked reduction of extraction (23, 24).

Analysis of the differences between arterial and renal venous concentrations of various relatively nondiffusible substances during an equilibration period can yield information regarding the distribution and time-course of flow. The difference in concentrations from moment to moment may be attributed (*a*) to the total volume of blood in the kidney in which the substance is diluted and (*b*) to the delays imposed by different parts of the vasculature in the passage from artery to vein. Green (25) has used T-1824 and Lilienfeld *et al.* (26) have worked with radio-iodine labelled human serum albumin and Cr^{51}-tagged red cells. Both workers have collected the total renal venous effluent in order to avoid the effect of recirculation. In similar studies of the splanchnic circulation Wheeler and his associates (27) have used a method that makes this unnecessary.

In order to evaluate pressure gradients within the kidney, Bruns and his associates (28) have thrust an intravenous catheter deep into the substance of the kidney, presumably occluding the interlobar veins, to measure the pressures in the arcuate veins and in this way to approximate pressures in the peritubular capillaries and interlobular veins. Intrarenal pressure has also been measured by thrusting a needle into the substance of the kidney and determining the pressure at which fluid neither moves into or out of the needle (29, 30). The needle is a veritable "crowbar" in the renal substance and in disrupting tubular, glomerular, and vascular structures yields values of somewhat dubious origin (31). Gottschalk & Mylle (32) have made more exact determinations of pressure in the peritubular capillaries of the rat kidney by means of micropipettes put in place under direct observation.

Intrarenal Hemodynamics

The renal vasculature displays at once a tendency to maintain flow within narrow bounds over a wide range of perfusing pressures and a remarkable capacity for change in association with widespread systemic circulatory adjustments. In both phenomena, the rate of perfusion must be controlled by actively changing resistances which are apparently capable of "auto-regulation," on the one hand; and subject to extrarenal influences that operate in the interests of cardiovascular integration, on the other. The site and character of the intrarenal resistances and the routes followed by blood flowing through the kidney remain uncertain and disputed.

Renal vascular resistances.—The afferent and efferent glomerular arterioles have long been regarded as the major variable resistances, without final agreement regarding their relative importance. Anatomic and functional data may be cited to indicate that either is dominant (2, 33, 34). Recent studies (28) suggest that a resistance in the distal portion of the venous outflow system may also contribute markedly to postglomerular resistance. Gottschalk & Mylle (32) found that capillary and intratubular pressures directly measured in the rat are approximately equal (13 ± 2.4 mm. Hg) and not greatly different from the wedged renal venous pressure reported in man (28). Elevation in arterial or renal venous pressure did not affect intratubular and capillary pressures until the pre-existing pressure was exceeded. Thereafter, pressures all rose in a parallel manner to a maximum above which further increases in arterial or venous pressure had no further effect. The close association of capillary and intratubular pressures suggests that outflow from and distention of the tubular system may also play a role in determining blood pressure-flow relationships in the kidney, perhaps secondary to compression of the veins by dilated tubules or to glomerular arteriolar dilatation.

It seems unlikely that arteriovenous anastomoses play a role in determining intrarenal resistance, though the possibility repeatedly crops up in the literature. Following injection of a suspension of beads, 19, 30, and 38 μ in diameter, into the renal artery of dogs, an average of only 1.5 per cent of the 19 μ beads, 0.3 per cent of the 30 μ beads and 0.08 per cent of the 38 μ beads could be recovered from the renal vein [Piiper & Schürmeyer (35)]. Neither surgical denervation nor the intra-arterial administration of procaine, cyanide, or histamine increased passage of the beads. These data suggest that the blood perfusing the kidney must pass through a capillary bed, presumably including the glomeruli, but it does not follow that blood is uniformly distributed to the renal parenchyma.

Distribution of blood.—Recent work (25, 26) suggests that blood traverses the renal vasculature by a variety of paths, some very short and some exceedingly long. Redistribution of red cells and plasma also seems to occur within the kidney so that red cells pass through more rapidly than plasma. This phenomenon implies that the intrarenal red cell mass is decreased relative to the renal plasma volume, so that the hematocrit of the total volume

within the kidney is less than the arterial hematocrit. Thus the radioactivity detectable over the kidney of the cat following injection of radio-phosphorus tagged red cells is approximately one-half the activity over arterial blood alone (36). Orientation of red cells toward the axis of the blood stream as a result of laminar flow with a relative increase in the peripheral cell-free plasma layer would seem to account reasonably well for such an apparent dilution of blood in capillaries.

Pappenheimer & Kinter (36) believe the disparity is much larger in the kidney than elsewhere. They suggest that as a result of plasma "skimming," the innermost cortical arterioles are supplied chiefly by the peripheral plasma layer and the outer cortical vessels, chiefly by the central core of red cells, thus producing a gradient of red cell concentrations ranging from abnormally low values (say 10 per cent) in the deeper glomeruli to very high values (say 80 per cent) in the terminal superficial glomeruli. Cell-rich blood is believed to return to the veins by thoroughfare channels that bypass the peritubular capillaries. This hypothesis implies, first, a relatively rigid structural frame within which plasma skimming would occur without danger of turbulance imposed by pulsation, respiratory or other body movements and second, certain relationships between the main stream and branches which may not obtain in the kidney (37). However, resistance to blood flow in such a system could conceivably vary directly with perfusing pressure as a result of change in viscosity alone, thus accounting for auto-regulation without need for vasomotor change. Since viscosity of blood varies as the third power of the red cell concentration, small changes in the hematocrit of cell-rich blood would have a much larger effect upon viscosity than similar changes in cell-poor blood. Thus, more efficient separation of cells and plasma at high perfusing pressures would result in a relatively larger proportion of cell-rich blood and in a net increase in viscosity (or resistance to flow) without any vasomotor adjustment.

Unfortunately, the authors' attempt to provide a sound factual basis for this interesting idea has not been very successful. In view of the scatter of the data, the uncertain significance of the average differences, and the lack of appropriate controls, it is difficult to accept their claim (33) that the intrarenal hematocrit varies inversely with pressure or that it tends to approach the arterial hematocrit at low pressures. The authors seem to assume that the production of anemia by removal of blood and replacement by plasma and dextran solution has no effect upon the renal vasculature other than that attributable to the change in hematocrit. However, according to the data presented (36), a much larger volume is introduced than is withdrawn, and it is possible that hypervolemia may account for some of the results at variance with the work of others recently (38, 39) and in preceding years. The data strongly suggest that the renal extraction of sodium *p*-aminohippurate or Diodrast is reduced in the anemia produced in these studies as the result of hyperemia rather than perfusion of channels bypassing the peritubular capillaries, as the authors believe. Severe anemia

may also have resulted in altered tubular function. It is impossible to assess the data presented (36) on this point owing to the lack of information on methodology and on load-transfer relationships. Finally, the authors' claim (40) that "auto-regulation" in the excised perfused kidney was "partly or wholly abolished at low red cell concentration" and returned with restoration of the cells is not entirely borne out by their data. The change in blood flow does appear to be somewhat less in the kidney perfused with red cells in dextran solution but the percentile difference is not as large as the linear scale makes it appear. Rejection of the somewhat excessive speculation based on these data should not detract from the value of the concept the authors have put forward. The possibility of a change in viscosity (and vascular resistance) solely as a result of nonuniformities in the distribution of cells and plasma is deserving of careful consideration in the evaluation of any hemodynamic readjustment. Until further evidence is available, however, the low intrarenal hematocrit may be attributed to "stream-line flow" within a rich vasculature of small vessels distended by blood under pressure.

In addition to these aspects of the distribution of blood in the kidney, relative renal vascular engorgement is evident in the intact animal, not only in measurements of intrarenal pressure, but also in the fact that an average of 14.5 ml. drains from the excised canine kidney, or more than 27 ml. per 100 gms. of tissue [Swann, *et al.* (41)]. The hematocrit of the run-off is only 63 per cent of the arterial, indicating dilution of each milliliter of blood by 0.62 ml. of a cell-free fluid which contains approximately the same amount of sodium and calcium as arterial plasma, 50 per cent more potassium, 20 per cent more chloride, twice as much phosphate and much less protein (30 per cent), glucose (40 per cent), and inulin (50 per cent). If the diluent is indeed derived from the intersitial fluid, the interstitial volume is "13 per cent of the renal volume or some 20 times greater than capillary volume" (41). However, a period of some 15 minutes is required for complete drainage, ample time for movement of fluid from the tubules, and the composition of the diluent is not unlike that of tubular urine, particularly if it is assumed that the protein content may be ascribed to cell-free plasma within small vessels. The lack of correlation with urinary composition is not surprising since the fluid in the collecting ducts to which urine concentration is referable constitutes but a small fraction of the liquid available within the tubules. Hence the actual volume of excess blood in the renal vasculature is uncertain. Additional study is required to assess more accurately the extent and localization of blood volume in the renal vasculature.

Regulation and Response

Neural and humoral mechanisms.—Neural and humoral mechanisms seem to control the initiation, integration, and perpetuation of renal vascular responses. Acute denervation of the kidney, transplantation, or autonomic blockade tend to induce a slight increase in renal blood flow, if blood pressure does not fall, and to interfere with appropriate reactions, at least temporarily

(42 to 48). With unilateral denervation the rise in blood flow has been found to result from release of vasoconstriction that persists in the control kidney and that is evidence, therefore, not of tonic activity but of a response to anesthesia, trauma, and the like. Auto-regulation is less effective and flow may change with pressure as much as 100 per cent (49, 50), but it never changes as much as the perfusing pressure (2, 33). A prolonged period of denervation may result in more marked interference with vascular autonomy (49), although local mechanisms usually appear to be capable of maintaining tone and responsiveness (44). Local antidromic or "interoceptive" reflexes may play an important role [Bálint *et al.* (50)]. The chief difficulty for this thesis lies in the lack of convincing anatomic evidence of intrarenal baroreceptors, although renal vascular resistance does seem to change as a consequence of manipulation of the vessels in the renal pedicle (51, 52). Impulses arising in the urinary tract may also be involved (52).

Denervation does not necessarily imply complete cessation of central neural influence since the renal vascular bed may continue to respond to neurohumoral transmission (53). Epinephrine and norepinephrine appear in the urine under a variety of conditions (53 to 56), presumably chiefly as a result of adrenal medullary activation. Humoral agents released by the adrenal cortex and the pituitary also seem to be involved in renal vascular regulation. Adrenal cortical damage by Rhothane [1,1-dichloro-2,2-bis (*p*-chorophenyl) ethane] or hypophysectomy results in a reduction in renal blood flow without change in arterial pressure (57). Little, Kelsey & Yount (57) have confirmed earlier work showing that ACTH causes intrarenal vasodilation in the normal dog and have found that it restores renal blood flow to but not above the control level following Rhothane.

Agents elaborated within the kidney itself may contribute not only in local responses but also in systemic hemodynamic adjustments. Renin appears to be one such substance and there may well be others (58). Renoprival hypertension, in which renin does not seem to be implicated (59), may thus arise from the lack of some vasoactive material usually produced by the kidney or to retention of an as yet unidentified pressor substance (60). Bilateral nephrectomy seems to increase systemic circulatory reactivity to norepinephrine (61), possibly because the kidney exerts a buffering influence of some kind.

Changes in the volume and chemical composition of the extracellular environment are also associated with intrarenal hemodynamic adjustments that bring about appropriate changes in filtration. Whether these changes can act directly upon the renal vasculature or indirectly through the mechanisms already mentioned remains disputed (62). The evidence available does little more than indicate some of the agencies involved in renal vascular regulation. Just how they operate, how they are interrelated and balanced, or how they evoke a response appropriate to the stimulus remains unknown.

The patterns of response.—These are notably diverse and difficult to evaluate. Intrarenal vasoconstriction appears to occur most commonly, usually

as part of a systemic vasoconstrictive reaction. In hypothermia, for example, the obvious dermal vasoconstriction in dogs and other experimental animals is associated with a profound reduction in renal blood flow (63, 64, 65). It may be preceded briefly by vasodilatation in the early phases as the temperature begins to fall and shivering begins. Mediation by the nervous system seems likely, at least initially, since chilling a single extremity alone will elicit intrarenal vasoconstriction presumably by neural stimulation (66), though humoral agents may also play a roie, since steroid output by the adrenal cortex is increased (67). In addition, physical factors such as the temperature, hematocrit, and viscosity of the blood perfusing the kidney probably contribute. When vasoconstriction is long maintained, it seems capable of producing severe parenchymal damage, possibly, though by no means certainly, related to prolonged anoxia. Interestingly, fatty infiltration of the tubules is striking in dogs (68) following hypothermia, whereas tubular necrosis marked by absence of lipide is characteristic of the effect of temporary (1½ to 4 hours) complete ischemia in rabbits (69). This difference may be explained by differences in duration and severity of the ischemia, in the chemical environment of the tubular cell, or in the species.

A variety of conditions in which intrarenal vasoconstriction develops seem to have in common a deficit in "circulating blood volume" (or inadequate venous return and cardiac output relative to need) so that arterial pressure tends to fall. Assumption of the upright posture, anemia, and hemorrhage (or traumatic shock in general) are similar in this respect as studies during the past year have shown again (38, 43, 70, 71). On the basis of studies upon the effect of increasing the pressure in the left atrium (mitral orifice obstruction by balloons), pulmonary vasculature (ligation of the pulmonary veins) and the pulmonary arterial tree (embolization) of dogs, Henry, Gauer & Reeves (71) conclude that stretch receptors in the left atrium, activated by changes in atrial filling, may be concerned in producing the response to hypotensive states. Unfortunately, in experiments of this kind it is difficult to eliminate effects produced by baroreceptors elsewhere. The adrenal medullary hormones are released during hemorrhage and orthostasis (53, 56, 72) but are not known to contribute in the more slowly developing, persistent, and prolonged response to chronic anemia. Exercise also elicits intrarenal vasoconstriction (73), possibly on the same basis as orthostasis and hemorrhage, since the rise in cardiac output is not commensurate with the increment to flow in exercising muscle so that arterial pressure would fall if compensatory intrarenal vasoconstriction did not develop. Perhaps a similar situation accounts for the fall in renal blood flow when a large arteriovenous shunt is opened suddenly, though measurements of central venous pressure show little change (74). Apnea, on the other hand, seems clearly to evoke vasoconstriction in the kidney of the rabbit by way of the vagus since the response is blocked by atropine or denervation (75). The renal blood flow also decreases in response to elevation of renal venous pressure [abdominal compression (76) or pregnant uterus (77, 78)] or renal

pelvic pressure (79), presumably as a result of the change in pressure gradient, though intrarenal vasoconstriction may also contribute.

Vasodilation develops in response to a fall in arterial pressure produced by veratrum viride (80) or reserpine (81) apparently as a manifestation of "auto-regulation." Hypotension produced by orthostasis or blood loss does not elicit a similar response. In fact, vasodilation is encountered infrequently, though a number of drugs [magnesium sulfate (82) and hydralazine as well as pyrogen (83)] appear to be capable of acting directly on the renal vasculature to induce dilation. As information regarding the behavior of the renal circulation accumulates, more clear-cut patterns of response and more definite systems of integrating and controlling mechanisms should emerge. At present the data are fragmentary, the picture clouded, and a definitive synthesis quite impossible.

GLOMERULAR FILTRATION

Urine formation seems quite certainly to begin within the glomeruli by the separation of water and solutes from the plasma by a process which is generally regarded as ultrafiltration. Variability in nephron size (84) strongly suggests a corresponding variety in individual glomerular filtration rates and presumably also in the distribution of the total filtrate among the population of tubules. Since the volume of filtrate may condition tubular function, precise information regarding the dynamics, disposition, and regulation of glomerular activity is essential to an understanding of urine formation.

Methodology

The inulin clearance is widely accepted as a satisfactory measure of glomerular filtration in man and experimental animals; creatinine clearance in most species other than man (8). Inulin is a vegetable polysaccharide (dahlia, artichoke) which consists of at least two fractions, one characterized by a relatively large molecular weight and resistance to heating in alkaline solution, the other by smaller molecular weight and "alkali-lability." Walser, Davidson & Orloff (85) have found that the clearance values for the two fractions are identical in man. Filtration of inulin (dahlia) fractions at different rates may account for a progressive fall in clearance values observed in man during 24 to 48 hours after intravenous administration of 0.9 to 5 grams [Barnard, Bassir & Hough (86)]. Retention of the large molecular fraction would then result in predominance of the large molecular clearance value. These results may be attributable to analytical error and difficulty in correcting for "inulinoid blank" at the very low plasma levels, all less than 0.12 mgm. per cent, since the "good chemical recoveries" reported (86) were obtained at a concentration of 10 mgm. per cent. Another finding possibly explained by molecular inhomogeneity is failure of complete excretion of inulin from the body. Although earlier work indicated complete recovery within 24 hours after a single intravenous injection, as much as 34

per cent of the dose was retained in the patients studied by Barnard and his associates (86). Reinfusion of urine during an inulin infusion over a period of five hours also resulted in a reduction in recovery, only 86 per cent on the average for "yeast-resistant" inulin and 80 per cent for "alkali-stable" inulin [Deane & Smith (87)]. This method does permit evaluation of inulin metabolism in the body when kidney function is normal, but a very small loss of the concentrated urine during collection and transfer may have introduced a sizeable error.

The identity of creatinine and ferrocyanide clearances with inulin clearances in the dog has been questioned by Ladd, Liddle & Gagnon (88). In control studies the ratios of creatinine and ferrocyanide clearances to inulin averaged 0.936 ± 0.047 and 0.932 ± 0.059 respectively. A survey of previously reported work suggested that the discrepancy may have been overlooked as a result of compensating analytical errors. The clearance ratios remained unchanged as long as inulin clearance exceeded 2.3 ml. per min. per kg. ("lower limit of normal"). Reduction in filtration rate by renal arterial hypotension (hexamethonium, hemorrhage, or compression of the aorta) resulted in a fall in the ratios which proved reversible with restoration of the renal arterial pressure or increased urine flow (osmotic diuresis). This phenomenon was not effected by the administration of probenecid (Benemid) or phloridzin. The authors conclude that "partial permeability of the normal renal tubule allowing passive back diffusion" of the smaller molecules of creatinine and ferrocyanide accounts for the discrepancy. In view of the increasing evidence of heterogeneity, comparison of different inulins under these conditions seems in order. Addition, rather than loss, of creatinine within the tubules of the frog is claimed by Swanson (89), though it is difficult to compare his findings with earlier work owing to his use of anesthesia, surgical manipulation, perfusion, and blood sampling from a "cutaneous vein" as the basis for clearance calculations. Nonetheless, the data do suggest active tubular secretion of creatinine. Good agreement between creatinine and inulin clearances in the rat have been reported by Gribetz, Van Loon & Crawford (90) though the comparison was not extended over a full range of urine flow. Similarly it is difficult to evaluate the most recent method (21) suggested for calculation of the glomerular filtration rate from the change in plasma concentrations following a single injection of creatinine.

Dynamics of Filtration

The mechanics of the transfer of fluid from the plasma to the glomerular space is not susceptible to direct investigation but must be approached by indirect methods. At present the evidence seems best explained by a process of filtration across the featureless membrana propria through interstices of the fenestrated endothelial lining and between the pedicels of epithelial cells. However, Chinard, Vosburgh & Enns (91) argue [not without opposition (92)] that there is diffusion across the total surface and not "bulk filtration" through pores in the membrane. They base their view largely on

theoretical grounds, defining diffusion thermodynamically as passage across the glomerular barrier under gradients of chemical potential for neutral substances and of electrochemical potential for ions. Chemical and electrochemical potentials refer to the partial molal free energies of the substances under consideration and are determined by concentration, temperature, pressure, and membrane potential. Diffusion defined in these terms may account for the formation of glomerular fluid having the composition of an "ultrafiltrate" on the assumption that rapid movement across the membrane of highly diffusible substances (and water in particular) will so affect the concentrations or chemical potentials of the remaining less diffusible materials that the net rates of transfer will be essentially the same for all. They bring forward no evidence to support this view or the assumptions on which it is based, but present data indicating that diffusion is an important determinant of the movement of solutes and water from the blood perfusing the entire kidney. A mixture of test substances, including urea, thiocyanate, inulin, xylose, sodium *p*-aminohippurate, Na^{24}, K^{42}, THO, DHO, and T-1824, was injected into the renal artery of anesthetized dogs and concentrations in renal venous blood, were determined at one to four second intervals. Comparison of the recoveries of different substances with that of T-1824 (assumed to remain in the plasma) reveals escape from the blood in a manner suggesting that large molecules move less rapidly from the blood into the interstitial space than small ones. Even if diffusion plays a dominant role in determining the movement of each substance into its respective total "volume of distribution," "bulk filtration" may still constitute one step in the process. Certainly the formation of glomerular fluid must contribute relatively little to the overall picture.

The glomerular membrane appears to be relatively impermeable to molecules as large as the plasma proteins. Although approximately 4320 grams of protein pass through the glomerular capillaries each day, only some 70 mgms. (resembling serum α-globulin) are excreted in the urine [McGarry, Sehon & Rose (93)]. Even this figure is open to question since most of the protein in the urine of normal persons may be secreted by the mucosal cells of the urinary tract (94, 95). Electron micrographs of dialyzed urine show particles of at least five colloidal substances (96), including mucoprotein, that may interfere with determination of the small amount of protein normally in the urine in man. When overt proteinuria occurs, it is usually abnormal. Even in so-called "benign proteinuria," demonstrable renal disease ultimately develops in some 40 per cent (97). The causes of genuine "benign proteinuria" remain obscure.

If protein usually crosses the glomerular membrane, its absence from the urine may be construed as evidence of tubular reabsorption and proteinuria may be ascribed to a defect in tubular function rather than to increased glomerular permeability. Malmendier & Lambert (98) have confirmed earlier work in showing that elevation of the plasma protein concentration in a dog (repeated plasma transfusions) resulted in persistent urinary loss of

protein having the character of plasma proteins. No change occurred in filtration and renal blood flow. The concentration of protein in the glomerular filtrate and the maximal tubular reabsorption of protein (protein Tm), calculated from the linear relation between protein concentration in the plasma and excretion in the urine, amounted to 24 mgm. per cent and 10.5 mgm. per min. respectively. Considerable uncertainty characterizes computations of this kind since very small errors in determination may cause large shifts in the slope and intercepts of the regression line. Equivalent protein filtration in man would require the reabsorption of about 35 grams of plasma protein per day. Failure of reabsorption would then readily account for heavy proteinuria. Proteins such as hemoglobin and egg albumin (99) seem to accumulate in the tubular cells as droplets. It is difficult to believe that such a large mass of plasma proteins could be transferred by or metabolized in the tubules of the human kidney without some evidence of droplet formation. The normal proteinuria in the male rat is associated with demonstrable droplets in the proximal tubules (100). It is augmented by urea and increased protein intake possibly because urea may interfere with tubular absorption of globulin (101, 102). The proteinuric effect of renin, egg albumin, hemoglobin, human serum albumin, sub-total nephrectomy, or renal venous congestion seems to be attributable to increased glomerular permeability in both rats and dogs (103 to 107). Löwgren (108) has recently suggested that benign proteinuria arises from escape of renal lymph into the urine within the renal pelvis. Since creatinine and protein excretion are not necessarily correlated, he concludes that the glomeruli are not implicated in protein loss. However, such small changes in glomerular permeability are required that filtration rate need not be measurably affected and failure to find a correlation is therefore not very significant.

Distribution of Filtrate

Growing evidence (84) of heterogeneity of the nephron population has suggested the possibility of an equivalent heterogeneity in glomerular filtration rates and in the times required for molecules to move from the glomeruli to the bladder. Two approaches to this problem have been made; one, applicable in man and intact animals, by which excretion in the urine of inulin and other substances is compared with the amount brought to the kidney each minute (109), and one in which an injection is made directly into one renal artery and comparison of urinary excretion at 12 to 30 second intervals by the two kidneys used to eliminate the effects of recirculation (110). Owing to the need to assume a steady state throughout and the large effect of small analytical errors, inferences must be drawn with great caution. Thus it seems somewhat premature to accept the view that calculated transit times for urea or sodium shorter than those for inulin imply tubular secretion of these substances (110). Relatively small changes in reabsorption at the time of injection could have a similar effect. The data are consistent with nonuniformity in the distribution of filtrate of the nephrons; i.e., some

get more, some less than others. Both direct and indirect (8, 32) evidence indicate persistent filtration in the mammalian glomerulus. Filtration does vary, of course, with changes in blood flow as noted above and at times may cease altogether in a fraction of glomeruli when the provocative stimulus is marked. Maximal glucose reabsorption by the tubules (glucose Tm) serves as a guide to such a change. This is implicit in the data reported by Dempster, Eggleton & Shuster (111). Since filtration and glucose reabsorption decreased in dogs during determination of glucose Tm, they concluded that "variation in the capacity of the tubule cells to reabsorb glucose robs the term 'Tm' of any particular meaning." However, these changes occurred only at very high levels of plasma glucose (more than 1000 mg. per cent) in association with hyponatremia and excessive diuresis that might well have altered filtration and nephron participation in reabsorption. The erratic behavior of the phosphate Tm in some subjects has also been attributed to irregularities in filtration by Longson and his associates (112).

WATER EXCRETION AND OSMOREGULATION

Renal water excretion is exquisitely adjusted to maintain the tonicity and volume of the body fluids within narrow limits. The formation of hypotonic or hypertonic urine in accord with need appears to depend upon the integrity of tubular mechanisms of water reabsorption and neurohypophyseal function. Most of the water in the glomerular filtrate probably returns to the blood by passive diffusion in the wake of solute actively reabsorbed in the proximal segment (8). The residue entering the distal segment for further processing is believed by Smith (8) and others (113) to be iso-osmotic as a result of equilibration during passage through the thin limb. An alternative possibility that it may be hypotonic is indicated by a fall in urinary osmolarity below, rather than to, plasma osmolarity during an osmotic diuresis in patients with diabetes insipidus who have received just enough vasopressin to make the urine slightly hypertonic [de Wardener & del Greco (114)]. In any case, the formation of very dilute urine seems also to require reabsorption of solute alone from the residual urine in a distal portion of the tubule which is impermeable to water (8, 115). Water secretion seems unlikely though D_2O has been shown (116) to move by diffusion from the renal portal blood into the tubular lumen in the bullfrog. Ussing & Andersen (117) have found that vasopressin increases the permeability of frog skin to water, possibly by altering pore size, and it is conceivable that a similar action on the distal tubular epithelium would permit back-diffusion of water. This would not result in osmotic concentration, of course, but it would markedly reduce the volume of tubular urine left to enter the collecting tubules, where accumulating evidence (8, 115) places the urinary concentrating mechanism. Smith and his associates (8) have proposed a continuous reabsorption of water alone in this region at a rate ($Tm^{C}_{H_2O}$) up to a maximum of some 5 to 7 ml. per min. in man as the basis for osmotic concentration. The mechanism of water reabsorption is quite obscure though it seems to

be resistant to the action of mercurial diuretics (113). The reabsorption of water would be limited not only by $Tm^{C}_{H_2O}$ but also by an osmotic ceiling, the maximal osmotic U/P ratio. Thus 5 ml. could be removed from a large volume of residual filtrate without appreciably affecting urinary concentration whereas removal of 3 ml. from 3.2 ml. could result in a maximally concentrated urine.

In keeping with this hypothesis, del Greco & de Wardener (118) have found that reduction in filtration rate by partial occlusion of the aorta or by inhalation of cyclopropane in dogs during a maintained water diuresis results in hypertonicity of the urine and oliguria which is rapidly reversible. Berliner & Davidson (119) have reported similar findings in a more elegant and conclusive experiment in which one renal artery was compressed in trained unanesthetized dogs so that the "physiologic diabetes insipidus" could be shown to persist in a continued diuresis by the unaffected kidney. In normal human subjects, also, filtration seems to be directly related to maximal urine flow and to "free water" excretion, and inversely correlated with maximal urinary osmolar concentration during water diuresis, as expected *ex hypothesi* (120). In this view glomerulotubular and intersegmental balances, i.e., load relative to the tubular or segmental reabsorptive capacity, must play a major role in determining urine flow and osmolarity. Imbalance may therefore be as important as tubular damage in causing defective water excretion. Thus, fixation of the urinary specific gravity in the course of renal disease is attributable not to a selective tubular lesion, since Tm_{H_2O} remains normal relative to filtration (121), but rather to an imbalance that results in excessive residual tubular fluid. Experimental evidence now obtained in man (122, 123) as well as animals suggests that diabetes insipidus is a similar manifestation of an imbalance arising from deficient secretion of antidiuretic hormone (ADH). Whether the so-called "nephrogenic diabetes insipidus" is an analogous and related (124 to 129) condition in which vasopressin does not enhance tubular permeability to water or a totally different disorder of tubular water reabsorption remains unsettled.

Antidiuretic hormone appears to be elaborated in the hypothalamus and stored, after transfer along the stalk, for release from the posterior lobe of the hypophysis (130 to 133). The neurosecretory and pituicyte theories of ADH origin may be reconciled in the establishment of the pituicytes as important agents in release. Release of ADH is presumably determined chiefly by changes in plasma osmolarity but other determinants, including some function of the volume of the body fluids (64), cannot be dismissed. Du Vigneaud and his associates (134) have synthesized lysine-vasopressin, an octa-peptide having oxytoxic, avian depressor, milk-ejecting, mammalian pressor, and antidiuretic actions. Lysine-vasopressin appears to be peculiar to the hog; arginine replaces lysine in vasopressin elaborated by man, macaque monkey, dog, rat, sheep, and camel (135). Many of the contradictions in the reported effects of ADH upon electrolyte and water excretion may be more apparent than real, possibly referable to differences in species

or dosage levels or to the effect of impurities such as histamine-like materials (136, 137, 138). Of particular importance is the total physiologic setting within which antidiuresis takes place. Hydration, available electrolyte mass, the activation of other endocrine systems, and the status of small cardiovascular adjustments are all involved in conditioning the response to ADH. A small reduction in filtration rate may thus account for the higher urinary concentrations attained during hydropenia alone than during the administration of vasopressin in well hydrated subjects (139). At times, indeed, as in evaluation of the antidiuresis produced by morphine (140), the combined effect of intrarenal vasoconstriction and release of ADH are not easily disentangled.

It may be equally difficult to assess the relative importance of an increment in filtration and of diminished ADH activity in causing diuresis. The correction of delayed water excretion in adrenocortical insufficiency by cortisone, but not by DCA, may be attributed to the rise in filtration produced by the former and not by the latter, to an effect of cortisone upon the tubular cells, or to both (141, 142). On the basis of a study of a patient with coincident Addison's disease and diabetes insipidus, Skillern, Corcoran & Scherbel (141) conclude that water diuresis is determined primarily by the level of the glomerular filtration rate. Study of diuretic responses in treated and untreated adrenalectomized dogs have convinced Garrod, Davies & Cahill (142), on the other hand, that a tubular change must be implicated because "peak urine flow" may be increased prior to a rise in filtration. Since circulatory effects are so important, the fact that vasopressin itself has a vasomotor action, apparently accentuated in patients with orthostatic hypotension (143), may be significant.

Recent work (144, 145) strongly suggests that a normal potassium content of the body (or more particularly of the renal tubular cells) is essential for a normal response to vasopressin. Potassium deficiency has been found by Hollander and his associates (144) to be uniformly accompanied by diminished ability (i.e., to 70 per cent of control) to form concentrated urine, even when the muscle potassium deficit amounts to no more than 10 per cent. Dilatation of the thin loop and marked cellular vacuolization in the collecting tubules seem to occur in both animals (145) and man (146, 147). Vasopressin appears to enhance the secretion of sodium, potassium and chloride (135, 147), suggesting the possibility that the anatomic changes of potassium deficiency point to an electrolyte transfer system under vasopressin control. Indeed, the natriuretic effect may be so pronounced when large doses are given, that diuresis rather than antidiuresis is induced (148).

RENAL EXCRETION OF ELECTROLYTES

The tubules are capable of dealing selectively with each electrolyte in the glomerular filtrate so that excesses or deficits of any single species are usually reflected in a prompt and appropriate elimination or conservation.

Nonetheless, the requirements of electroneutrality and the effects of potential differences and osmotic equilibria between cells and extracellular fluid lead to a complex ionic interdependence that has made analysis of electrolyte excretion peculiarly difficult. A great deal has been accomplished in recent years, as indicated to some extent in the symposium on this topic edited by Shanes (149), by a more sophisticated application of modern physicochemical methods and concepts. Ionic movements through membranes and into cells have been more sharply defined in terms of electropotential differences and concentration gradients so that the contribution of "active transfer" may be more accurately evaluated. Even so, it is extremely difficult to ascertain primacies in transfer, to say with certainty whether any given ion is moved actively by a specific system or passively as the result of potential differences generated by selective uptake of other ions.

Since the composition of the medium (tubular urine or capillary plasma) must also influence uptake, it is necessary to know how the filtrate changes as it moves along the tubule. Some light has been shed on localization of electrolyte transport by studies of the isolated nephron (150) and radioautographs (151). The use of renal portal venous perfusion of the bullfrog kidney (116, 152) has also proved helpful, but interpretation of the results in general terms must be guarded owing to the effects of anesthesia, surgery, and possible differences between animal species. Indeed, the latter possibility arises repeatedly in the appraisal of the data available on the renal excretion of electrolytes.

Recent work of Pitts, Berliner, Gilman, Darrow and many others has focussed attention upon ion exchange, sodium for hydrogen or potassium ion, sodium for ammonium, and the like, as one process by which transfer is effected. Although "ion exchange" simply denotes what seems to take place and does not indicate the precise mechanisms involved, the phenomenon points to an area in which research may be profitable. Moreover, the fact that similar exchanges occur in the cells of other tissues suggests that the mechanisms involved in renal tubular transport may not be unique but rather so oriented and so environed that excretion results. The extracellular environment of the renal tubular cell is distinctive in that a large fraction (that within the lumen of the tubule) has little opportunity of coming to equilibrium with intracellular fluid. Hence, the rate of movement along the tubule and the character of the prevailing disequilibria may well affect the ultimate urinary composition. Be this as it may, the parallel between tubular cells and tissue cells in general has proved extremely fruitful in suggesting experimental approaches.

Cation Excretion

Sodium.—Sodium transfer by ion exchange appears to dominate in determining the urinary sodium content particularly in relation to hydrogen ion excretion, suggesting that exchange occurs in the lowermost reaches of the tubules but that the bulk of the filtered sodium is transferred by a specific

carrier system in the proximal segment (153 to 157). In addition, Smith (8) postulates a third limited process (T^d_{Na}) in a portion of the distal segment impermeable to water by which sodium (and anion) transfer produces a dilute urine.

Possible mechanisms of specific ion transport or of ion exchange remain obscure and vague. A study of Hoshiko, Swanson, & Visscher (152, 158) of radiosodium transport in the perfused bullfrog kidney over a temperature range from 6 to 20°C. indicates a bidirectional flux of sodium across the tubule with a net rate of reabsorption that is a linear function of temperature, independent of the filtered load. The activation energy for the "active" sodium flux (24,600 to 34,400 cal./mole) calculated from these data appears to be consistent with a carrier system [analogous perhaps to that suggested recently by Thomas (159)] in which diffusion of a sodium-carrier complex is the rate limiting step. The general application of these observations is doubtful for the reasons mentioned above. Bidirectional sodium flux detectable in the bullfrog kidney (152) may be an expression of reversible processes concerned in ion exchange.

Just how sodium is taken up for transfer is not elucidated by any of these investigations. A number of hypotheses to explain uptake have been advanced by Conway, Ussing, Robinson, Davies and others on the basis of studies of transfer across frog skin and other membranes (149). In the "redox hypothesis," for example, electron transport is considered primary and movement of ions is believed to be dependent upon an appropriate organization of oxidative enzyme systems within the membrane. The "dual pump mechanism" depends upon two hypothetical "ion pumps" separated spatially within the cell and working in sequence; an "adsorption-desorption pump" to maintain intracellular ion differences and a "redox pump" to provide for transport across cell boundaries (160). All these schemes depend upon unproved assumptions regarding the state of ionization within the cell, the character of intracellular movements, and contributions of other cellular constituents that are not easily submitted to examination.

The evidence that ion exchange may hinge upon changes in intracellular hydrogen ion concentration is wholly indirect. Actual measurements of cellular pH are lacking. However, new data have been brought forward in the past year to show that potassium depletion (and presumably intracellular acidification as the result of potassium loss) results in enhanced sodium reabsorption [as such or as "bicarbonate-bound base" (157, 161, 162)], evident even under conditions of sodium loading (161), with a rise in hydrogen ion and ammonia excretion secondary to enhanced hydrogen (and ammonium)-sodium exchange. The converse situation seems to develop during potassium loading (154). Two further observations give support to interpretation of these responses in terms of an hypothetical change in intracellular pH. First, the urinary changes produced by potassium depletion may be prevented by respiratory alkalosis and those of potassium loading by respiratory acidosis (157, 161). In the former, a fall in the intracellular CO_2 content

may be presumed to counter the acidifying effect of potassium loss and in the latter, a rise in intracellular CO_2 apparently maintains pH in the face of potassium accumulation. Secondly, Roberts, *et al.* (157) claim that stimuli believed to lower intracellular pH (potassium loading, respiratory alkalosis, and inhibition of carbonic anhydrase) have an additive effect when imposed simultaneously in reducing tubular reabsorption of bicarbonate-bound base in animals. Falbriard, Muller & Engel (163) observed the same phenomenon in human subjects, whereas Fuller, MacLeod & Pitts (154) failed to produce it in the dog. Additional support has emerged from studies of potassium exchange.

Sodium reabsorption is extremely difficult to assess in quantitative terms owing to the very small amount of sodium relative to filtered load that appears in the urine. A small and insignificant error in the measurement of sodium excretion or glomerular filtration rate will affect the calculated reabsorption disproportionately. It is for this reason that measurement of the so-called "bicarbonate-bound base" is of value since variation in bicarbonate reabsorption can be followed with greater assurance. Moreover, bicarbonate reabsorption may denote a major fraction of sodium exchanged for hydrogen, though potassium reabsorption is also involved.

Potassium.—Potassium transfer is currently believed to consist of reabsorption of all (or almost all) of the filtered potassium in the upper tubule followed by secretion in the lower segments (164). The mechanisms involved are wholly obscure, though studies of cellular uptake of potassium and sodium or hydrogen-potassium exchanges between cells and medium *in vitro* indicate that both processes are dependent upon oxidative and phosphorylative activity (165). The close association of potassium and mitochondria within renal tubular cells suggests that these structures may be concerned in some manner with transport (166, 167). Recent work (156) again confirms the earlier finding that potassium secretion is interfered with by mercurial diuretics in amounts apparently sufficient to uncouple "phosphorylation from oxidation in rat kidney mitochondria" (168). As far as the composition of the urine is concerned, ion exchange is believed to determine potassium as well as sodium content with potassium competing with hydrogen ion for exchange (by secretion) with sodium. Further evidence that potassium is secreted by the normal renal tubules has been adduced in studies (154) of potassium loading in which potassium clearance was found to exceed the filtration rate. In addition, Black and his associates (169, 170) claim that the maintenance of a higher specific activity of potassium in the urine than in the blood following injection of radioactive potassium bespeaks entry of potassium into the urine only by secretion. They find that radioactive potassium is rapidly distributed within the total renal potassium mass both in and out of the cells and they believe that the isotope continues to enter the tubular lumen from the cells long after plasma concentration has fallen to very low values. However, earlier studies, as they point out, strongly suggest that the disparity between plasma and urinary specific ac-

tivities can be accounted for by intrarenal delay. Although this possibility is dismissed as a complete explanation, Black, *et al.* (169, 170) do not seem to have tested it by appropriate methods. Even if delay were shown to account fully for the phenomenon, it would in no way affect the hypothesis of potassium secretion but would rather suggest that secretion occurs in some region proximal to the point of greatest delay.

Much more convincing evidence of tubular secretion of potassium has resulted from an ingenious study by Orloff & Davidson (171) who used the renal portal circulation in the chicken for introduction of potassium salts into the peritubular circulation of one kidney by way of a leg vein. Comparison of urine from the "experimental" kidney with the urine from the opposite side permitted quantitative measurement of potassium secretion. It was proved that transfer was limited, reduced by a local elevation in carbon dioxide tension that enhanced hydrogen ion excretion (competitive inhibition), and blocked by mercury.

The complex interrelationship between potassium, sodium, and hydrogen excretion has been further elucidated in the past year. Sodium depletion results in a much greater outpouring of potassium during an acid load, presumably because potassium exchange for sodium is important in sodium conservation. This response was observed by Clarke, *et al.* (155) in three human subjects depleted of sodium and made acidotic with large doses of ammonium chloride. In a study of seven patients on low-sodium diets or adrenal steroids, Schwartz, Jensen & Relman (153) found that potassium similarly replaced sodium in the urinary mixture during the acute response to an infusion of sodium sulfate which acidifies the urine without affecting extrarenal acid-base balance. Depression of sodium output, in patients receiving sodium sulfate, as a result of tilting into the upright position is also associated with increased excretion of potassium, according to Epstein and co-workers (156). Potassium depletion, on the other hand, appears to permit escape of sodium in ammonium chloride acidosis (155); potassium conservation seeming, thus, to depend upon diminished secretion and exchange. It should be emphasized that potassium-sodium ion exchange appears to be neither uniform nor absolutely necessary in determining urinary base composition since the excretion of both cations increases with acid excretion or diuresis and mutual replacement is not in any constant proportion. Evidently, availability [e.g., potassium excess contrasts with depletion by reducing sodium output (154)] and acid excretion are among the factors that condition the potassium output and make it difficult to detect regularities in its behavior.

The reciprocity between potassium and hydrogen ion excretion has been interpreted as evidence of competition between the two ions for exchange with sodium. This phenomenon is most marked in potassium loading and depletion (154, 155, 161), but it is not exclusive since both hydrogen and potassium excretion may increase simultaneously as during orthostasis in patients receiving sodium sulfate (153). Possibly the intracellular hydrogen

ion concentration (or hydrogen ion available for secretion) plays an important role. In line with this possibility is the fact that carbonic anhydrase inhibitors diminish hydrogen ion output and increase potassium excretion and probably do so in association with a rise in intracellular pH (154, 157, 163, 172, 173). With potassium depletion, on the other hand, so-called "paradoxical aciduria" develops in the face of a metabolic alkalosis possibly because the pH falls within the renal tubule cells. Studies of bicarbonate uptake by potassium depleted slices of rabbit renal cortex *in vitro* with and without potassium in the medium have been reported by Anderson & Mudge (165) in support of this inference. With potassium depletion, the calculated "intracellular" pH or bicarbonate content (assuming an extracellular space amounting to 25 per cent of the total tissue mass) was reduced with respect to the external medium and ranged from 7.00 to 7.38 as the pH of the medium changed from 6.85 to 7.60. When potassium was added to the medium, the intracellular deficit was repaired and calculated "intracellular" pH was kept constant between 7.40 and 7.42 over the same range of pH of the medium. The crucial question, of course, is whether the potassium content of renal tubular cells is altered *in vivo*.

Iacobellis, Muntwyler and Griffin (174) failed to find any change in the potassium content of kidneys of potassium-deficient dogs; a slight though significant reduction was found in the kidneys of deficient rats (175). Hence, if potassium depletion does indeed produce aciduria by lowering the pH of renal tubule cells, only a portion of the tubule, a small fraction of the total renal mass, must be involved. The fact that prolonged potassium deficiency does induce lesions in the human kidney consisting of hydropic or degenerative changes in the convoluted tubules in association with vasopressin—resistant hypothenuria also indicates that renal tubule cells are involved (146, 147). Unfortunately, the electrolyte composition of renal tissue obtained from these patients has not been reported (146, 147). In any case, the disparities in the acute or chronic responses of different animal species and the obscure conditioning influence of the dietary supply of various anions and other cations (174, 175), as well as the lack of direct measurements, call for caution in assessing potassium excretion in terms of the chemical constitution of the cells.

Hydrogen ion.—Hydrogen ion transport cannot be discussed as a separate and distinct phenomenon since it is so completely dependent upon excretion of potassium, sodium, ammonium, phosphate, chloride, and bicarbonate ions as well as other factors that are even more difficult to define. Tubular secretion of hydrogen ions appears to account for the ability of the kidney to put out urine that is more acidic than the blood but little information is available regarding the mechanisms by which hydrogen ion is generated within the cell, moved from the cell into the tubular lumen, and maintained within the tubular urine thereafter against a concentration gradient.

Evidence continues to accumulate in favor of the view that carbonic anhydrase is active within tubular cells in making hydrogen ion available

for secretion (154, 157, 163, 172, 173). It is possible that "adaptative" increase in carbonic anhydrase activity contributes to compensation over prolonged periods of excessive acid intake or base loss (174), though under certain conditions (175) little correlation is evident. Indeed, it may be argued that the amount of hydrogen ion made available by carbonic anhydrase is not sufficient to account satisfactorily for the amount appearing in the urine (176). If carbonic acid is the chief source of hydrogen ion, the amount of titratable acid and ammonium excreted (a measure of hydrogen ion secretion) must be dependent upon the amount of carbon dioxide formed in the kidneys. Roberts and her associates (177) have found that the maximal capacity for secretion of hydrogen ion secretion in dogs is indeed limited, as expected on the carbonic anhydrase hypothesis, by renal blood flow and oxygen consumption. Carbonic anhydrase activity is not detectable in the kidneys of the dogfish (*Squalus acanthias*) or sculpin (*Myoxocephalus scorpius* and *M. octodecimspinosus*) though it seems to be important in renal acid excretion in the freshwater catfish (*Ameirus nebulosus*) (178). In the alligator carbonic anhydrase appears to be involved chiefly in anion excretion; inhibition results in acidification rather than alkalinization, and increased output of chloride rather than potassium or sodium (179). In contrast the turtle appears to respond to acetazoleamide (Diamox) like man (180).

Movement of hydrogen ion seems solely a function of exchange for sodium. It is possible that acidification of the cell under the influence of carbonic anhydrase (or some other system in which carbonic anhydrase participates) provides a gradient which promotes the transfer from cell to tubular urine. Increased sodium uptake certainly stimulates hydrogen ion transfer regardless of the requirement of the body economy as in response to tilting (156) or administration of poorly reabsorbable anion (153), a fact suggesting that alkalinization of the cell might play a role in mobilizing hydrogen ion. As noted above, hydrogen and potassium ion appear to "compete" for sodium though the output of both may increase simultaneously (156, 175), and both may be affected similarly by Diamox (156). Additional evidence that the "competitive" relationship between the two ions is not simple and stoichiometric is found in the lack of a fixed and uniform mole-for-mole substitution (154). Acidification appears to occur in the lower segments, at least in the amphibian (150); more precise localization of transfer in mammalian kidneys might be helpful in elucidating species differences (174, 175).

Ammonium.—Ammonium transfer appears to depend upon the pH of the urine and the activity of the synthetic mechanism within the tubule cells. Orloff & Berliner (181) have evaluated these factors quantitatively in the dog by comparing the excretion of ammonia and various weak bases including quinine, quinacrine (Atabrine), 9(diethyl-amino-1-methyl) butylamino acridine (SN8439), and 3-chloro-7-methoxy-9(diethylamino) ethylamino acridine (SN5228). Alkalinization of the urine by infusion of sodium bicarbonate uniformly depressed the outputs of ammonia and weak base; alkalin-

ization by administration of potassium chloride or Diamox diminished ammonia and quinine excretion similarly but did not affect SN8439 excretion consistently. The output of ammonia and weak bases remained constant over a wide range of urine flows as long as the urine was acid. At higher pH values (between 6.0 and 7.0) the rates of excretion seemed to vary with urine flow. These findings were interpreted as evidence that ammonia and other similar weak bases enter the urine from the tubule cells by diffusion as the free or singly charged base and are "trapped" in the acid urine by combination with a hydrogen ion to become the less diffusible lipide insoluble ionic species. Under these circumstances accumulation is limited by the maximal rate of ammonia synthesis or of diffusion of the exogenous bases, and urine flow does not, therefore, affect the excretory rate (though it does alter urinary concentration, of course). Since the concentration gradient is the difference between the concentration of free base (ammonia, for example) within the cell and its concentration in the urine, equilibrium is never attained at low pH but with alkalinization equilibrium can occur and the rate of flow of tubular urine becomes important as a limiting factor. The fact that even in alkaline urine ammonia excretion is more closely related to pH than to concentration is considered by the authors (181) to indicate ammonia secretion at some point in the tubule proximal to the site at which urine volume is finally determined. A similar correlation between urinary pH and ammonia output has been observed in human subjects receiving ammonium chloride (155), sodium sulfate (153, 156), and Diamox (156, 163, 172), suggesting that man and dog handle ammonia similarly.

In the rat, on the contrary, urinary pH appears to exert a negligible influence upon ammonia excretion (182), a fact responsible for some confusion and disagreement (172). Leonard & Orloff (182) have found that the urinary ammonia output is regulated chiefly by changes in body acid-base balance. Atabrine, in contrast, is excreted by the rat as a function of urinary pH regardless of the degree, duration, or source of acidosis. Ammonia falls as urinary pH rises during infusion of sodium bicarbonate, whereas alkalinization of the urine, as a result of acute or chronic administration of Diamox with the production of acidosis of body fluids, produces little or no change in ammonia excretion. The administration of sodium sulfate to sodium deficient rats resulted in only a slight increase in ammonium excretion (in contrast to man) whereas hydrochloric acid infusion has a profound effect in spite of much less marked acidification of the urine. In contrast to the effect of alkalinzation of the urine by potassium chloride in the dog (154, 181), infusion of potassium chloride into acidotic rats causes a fall in urinary pH without appreciably affecting ammonia excretion (182). This dissociation may be accounted for by differences in permeability of the tubular cell membranes or by changes in the rate of ammonia production within the cell. The relationships between pH and excretion in dog and man seem to imply a constant intracellular concentration of ammonia which either governs the reaction rate of a reversible enzymatic process or arises from an irreversible reaction

and is distributed variously with pH to urine and "metabolic pool." In the rat, on the other hand, intracellular ammonia concentration appears to rise with acidosis and fall with alkalosis, but there is insufficient evidence at present to indicate whether this is attributable to increased rate of formation or decreased intracellular utilization (182).

A similar independence of pH and ammonia excretion seems to be evident also in both dogs and rats in the adaptive augmentation in the output of ammonia during the course of chronic acidosis. There appears to be a fairly good correlation between glutaminase activity and ammonia production in both dog and rat (174, 175, 182) but the meaning of this association is by no means clear. Certainly the rat is capable of a marked increase in ammonia excretion immediately after imposition of an acid load and before a change in glutaminase activity is detectable. Nonetheless the role of glutamine as the major source of urinary ammonia strongly suggests that altered glutaminase activity is concerned in some manner with ammonia secretion, particularly in the adaptive phase. In the guinea pig Richterich-van Baerle, Goldstein & Dearborn (183) have found that ammonia output and concentration rises from low values at a urinary pH of 7.5 with both alkalinization and acidification of the urine, and they suggest that glutaminase activity may be a particularly important limiting factor in alkalosis. Ammonium is actually the most abundant cation in the very alkaline urine of the alligator, and it appears to be important in connection with osmolar and water excretion as well as base conservation (179). Presumably several mechanisms are involved in ammonia excretion, but it seems likely that these differences between species arise in differences of relative importance and organization of the same processes rather than in basic design.

The availability of precursor amino acids and possibly of other substances may also place a limitation upon ammonia production. Infusion of amino acids (including glutamine, DL-alanine, L-glycine, or aspartic acid) produced a rise in urinary pH in association with an increase in ammonia excretion in the dog, presumably as a result of augmented synthesis. As Orloff & Berliner (181) point out, exchange of ammonium ion for base cannot occur under these circumstances and they conclude that the replacement of hydrogen ion by ammonium may permit further secretion of hydrogen. Availability may actually prove to be critical under conditions of "acid stress." Clarke and his associates (155) believe that the impaired response in ammonia production to acidosis produced by ammonium chloride in sodium-depleted human subjects is attributable to the reduction in the supply of precursor substances by the fall in renal blood flow. This possibility was not tested, however, by examination of the effect of induced changes in flow or amino acid loading. Additional work is necessary to define more precisely the role of this factor in ordinary adjustments in acid-base regulation.

Calcium and magnesium.—Calcium and magnesium excretion is imperfectly understood owing chiefly to the difficulty of measuring the protein-bound, complexed, and ionized moieties in the plasma. Thus increased excre-

tion during the action of parathyroid hormone, Vitamin D, dihydrotachysterol (AT 10) and other agents may be due to diminished tubular reabsorption, increased filtration, or both. Williamson & Freeman (184) have found that the filtrable calcium fraction of plasma (parlodion membrane at fixed pH and CO_7—O_2 tension) does increase in metabolic acidosis, but tends to remain within normal limits during other acid-base disturbances associated with hypercalciuria. The tubular reabsorption of calcium appears to be inversely related to blood pH, plasma bicarbonate content, and sodium excretion (184). This relationship may account for the tendency for salt depletion to develop in the course of prolonged hypercalcemia and for the elevation in sodium and chloride output during infusion of calcium gluconate in man (185). The character of the urinary electrolyte composition is particularly important in relation to calcium excretion because increased output predisposes to stone formation in alkaline urine.

Recent work suggests that the solubility of calcium may be enhanced in some fashion by the excretion of mucopolysaccharide (94, 96, 186). Harrison & Harrison (187) have brought forward new evidence that citrate excretion also may play a role in stabilizing the urinary calcium in solution. They found that urinary citrate excretion fell abruptly following administration of Diamox in large doses (250 mg./100 gm. diet) to rats fed an alkaline ash, high calcium, low phosphorus diet. Apparently as a result of this change, calcium phosphate concretions were deposited in the renal tubules at the cortico-medullary junction. However, a low phosphorus, high calcium diet induces citraturia and the formation of calcium citrate stones in protein-depleted rats (188) and it is possible that some other action of Diamox is involved.

Magnesium excretion is of particular importance in marine forms since it is such an important constituent of sea water. Brull & Cuypers (189, 190) and Forster & Berglund (191) report that magnesium is actively secreted by the aglomerular kidney of the teleost (*Lophius piscatorius*). Very little is known about the renal handling of other heavy metals. The excretion of radioactive cobalt (Co^{60}) was studied in dogs by Lee & Wolterink (192, 193) during the past year with results indicating substantial filtration of an unbound moiety and tubular reabsorption of a large fraction of the filtered load.

Anion Excretion

Chloride.—This major nonvolatile anion in the urine in mammals is often regarded as occupying a mendicant position in which it closely parallels cation excretion. On the basis of the movements of chloride ion *in vitro* between medium and rabbit kidney tissue slices, Whittam (194) has concluded that active reabsorption of sodium and potassium in the proximal tubule is sufficient to generate an effective potential gradient for the passive diffusion of chloride from lumen to blood. Solomon's (195) measurements of electrochemical potential differences across the tubules by means of micro-

electrodes yield figures in accord with Whittam's calculations. Chloride reabsorption cannot be considered solely in these terms, however, since the presence of other anions in varying concentration and priorities arising from differences in "availability" depending upon the total situation may exert a powerful modifying influence on output. Anderson & Mudge (165) report that intracellular chloride is displaced by bicarbonate when potassium enters potassium-depleted slices of rabbit kidney immersed in medium containing potassium bicarbonate. It is possible that bicarbonate is absorbed in preference to chloride in the proximal tubular segment in the mammal though Giebisch (150) has found that the expected high proximal tubular urine/plasma concentration ratios for chloride previously reported on the basis of work with the isolated *Necturus* tubule can be explained by failure to deproteinize both serum and tubular fluid. Hilton, *et al.* (196) believe that chloride may be reabsorbed by the canine kidney in preference to bicarbonate under certain conditions because administration of chloride during respiratory acidosis results in a increase in bicarbonate excretion. Chloride excretion decreases during sodium sulfate loading in both normal and sodium-depleted subjects whereas bicarbonate excretion falls off only in the latter, suggesting, as Schwartz and his associates (153) point out, that bicarbonate and chloride do not compete for transport. It is quite impossible to assess the position of chloride relative to other ions in electrolyte transfer on the basis of the data available at present. Indeed, the available information is not altogether inconsistent with dominance of electrolyte movement by chloride ion.

Mercurial diuretics seem to interfere selectively with a discrete chloride transfer system and to depend upon chloride "availability" for an adequate diuretic response. Mudge & Hardin (197) have found that this relationship may be affected by an acid-base disturbance within the tubular cells. In potassium depleted dogs presenting hypokaliemia and hypochloremia, a normal diuresis followed administration of meralluride whereas acute metabolic alkalosis resulted in refractoriness to the drug despite maintenance of the plasma chloride concentration and glomerular filtration. They conclude that increased acidity of the renal tubule cells in potassium-depleted animals "facilitates the interaction between mercurials and cellular components of the electrolyte transport mechanism" (199). Changes in intracellular pH during potassium deficiency may also be involved in reducing chloride reabsorption. The tendency for rats to develop alkalosis more readily than dogs under seemingly comparable conditions of deprivation has been ascribed by Iacobellis *et al.* (174) to better maintenance of plasma chloride by the dog. If chloride is involved in urinary acidification, as these studies may suggest, the site in the tubule at which the mercurial diuretics have their action would be helpful in functional localization. However, this question remains unsettled. Recent work seems to favor the proximal segment because diuresis amounts to the addition of a large volume of isotonic fluid (hypothetically equivalent to proximal tubular urine) to the urine (113) and because plasma bicarbonate concentration at which titratable acid excretion begins to fall

(hypothetical proximal segment "bicarbonate threshold") is depressed (198). Since interpretation depends upon unproved assumptions regarding proximal segment functions, these findings cannot be regarded as conclusively supporting the belief that the action of mercurial diuretics is limited to the proximal segment. Nor have determinations of the disposition of mercurials tagged with Hg^{203} been much more helpful (199, 200, 201). Following intramuscular injection, radioactive mercury accumulates rapidly in the kidneys of dogs, rats and men provided there is no serious renal damage (201), and appears to be localized within the renal cortex, apparently bound within the cells in both the "soluble" and "granular" fractions obtained by homogenation and ultracentrifugation. According to Cafruny, Farah & DiStefano (202), intravenous administration of a mercurial diuretic causes a fall in the concentration of sulfhydryl in the cells of the terminal portions of the proximal tubules, ascending limbs of the thin segment, and the collecting ducts. Thus mercury may have three rather than a single site of action. Certainly the effect upon electrolyte transfer is not limited to chloride but also affects sodium, potassium, and bicarbonate ions as well.

Bicarbonate.—Bicarbonate excretion appears to be largely a function of acid-base excretion. There is much evidence (157) indicating that all the filtered bicarbonate is reabsorbed up to 2.4 to 2.8 mEq./100 ml. of filtrate and that all in excess of this amount is excreted. The character of the reabsorptive mechanism is not clearly defined. It is possible that bicarbonate uptake depends not upon a discrete reabsorptive system but rather upon the introduction of hydrogen ions in exchange for sodium, the carbonic acid thus formed decomposing and the highly diffusible carbon dioxide returning to the blood by diffusion, with reconversion to bicarbonate *en passage* under the influence of carbonic anhydrase (154, 157). As noted above, pH within renal tubular cells may play a role in determining bicarbonate transfer. A fall in intracellular pH as the result of elevated P_{CO_2} or potassium depletion promotes reabsorption, a rise secondary to depressed P_{CO_2} or potassium excess has the opposite effect (154, 155, 157, 161). These conditions seem to affect bicarbonate reabsorption at all plasma bicarbonate concentrations and are not limited in their action to change in the maximal transfer rate (154).

The possibility that bicarbonate uptake may also occur independently of carbon dioxide generation resulting from hydrogen ion exchange is indicated in (*a*) simultaneous increase in urinary pH, titratable acid, and bicarbonate excretion during infusion of potassium phosphate, (*b*) occasional diminution in bicarbonate output with potassium depletion in the absence of change in pH or titratable acid output, and (*c*) a normal maximal bicarbonate reabsorption in patients with renal insufficiency and diminished ammonia and phosphate excretion (157). Carbonic anhydrase inhibitors (163, 172, 173) presumably increase intracellular pH and simultaneously diminish hydrogen ion exchange. Schwartz, Porter & Relman (203) explain the action of very large doses of N-5-substituted acetazoleamide analogs,

which do not inhibit carbonic anhydrase, in promoting bicarbonate excretion as the result of their behavior as strong bases. In their view, tubular reabsorption of these compounds results in "binding" of hydrogen ion and reduces the amount available for exchange. Hilton and his associates (196) observed a fall in bicarbonate reabsorption during infusion of hypertonic saline solution in dogs with respiratory acidosis and concluded that "at least part of the reabsorption of bicarbonate" (which is ionic and not dependent upon hydrogen ion secretion) "is affected by reabsorption of chloride in such a manner as to suggest competition between the chloride and bicarbonate ions for a common reabsorptive transport mechanism." However, this conclusion is not warranted by the data presented since increased hydrogen exchange may have been expressed only in terms of increased excretion of acid buffers which were not measured. The constancy of the creatinine excretion is stressed by the authors as evidence that total buffer excretion did not change, but creatinine is excreted by filtration alone in the dog and is therefore a poor guide to tubular transfers of other buffers. Potassium bicarbonate or potassium chloride loading in dogs by Fuller *et al.* (154) produced roughly equivalent reductions in bicarbonate reabsorption, contrary to expectation if chloride actively competed with bicarbonate for transfer. The work of Anderson & Mudge (165) does indeed indicate that chloride and bicarbonate transfers are intimately related, chloride tending to follow sodium (and bicarbonate to follow potassium) in and out of the renal tubule cell under appropriate conditions of depletion and availability. No evidence of a discrete and specific intracellular transport system for bicarbonate is at hand.

When bicarbonate output is high and the urine very alkaline, the carbon dioxide tension is commonly higher in the urine than in the arterial blood perfusing the kidney. Administration of carbonic anhydrase to hydropenic dogs with mild metabolic alkalosis results in a prompt and significant fall in the urinary CO_2 tension to equality with the renal venous blood. Ochwadt & Pitts (204) regard this response as evidence that

> high tensions in alkaline urine must be caused by delayed dehydration of carbonic acid to carbon dioxide and consequent failure to attain diffusion equilibrium and not by the mixture of acid and alkaline urine in the renal pelvis.

However, their results do not preclude the possibility that acid and alkaline urine coming from different nephrons mingle in some portion of the intrarenal drainage system where back-diffusion of carbon dioxide is still possible. Wesson (205) has shown that solutions of sodium chloride (acid) and sodium bicarbonate (alkaline) placed in the temporarily isolated bladder of the dog undergo no change over a period of 25 to 80 minutes. Inward diffusion of hydrogen ions or decreased loss of CO_2 in the presence of alkaline urine cannot therefore account for the high P_{CO_2} of alkaline urine.

Phosphate.—Phosphate excretion varies widely as the result of the interplay of a large number of variables. Among these, changes in tubular reabsorption is of the greatest importance in determining adjustments in out-

put to the requirements of acid excretion and calcium metabolism. Phosphate is believed to be reabsorbed by a limited transfer system in man and dogs but the value of the transfer maximum (Tm) changes from day to day and from individual to individual is a seemingly erratic manner. Longson *et al.* (112) studied the relationship between plasma phosphate concentration and urinary phosphate excretion during phosphate infusion in five normal subjects on 23 occasions. In 15 instances, the plasma phosphate concentration and phosphate output were linearly related, the slope of the regression line yielding values for glomerular filtration in good agreement with simultaneous measurements of inulin clearance. This result is in harmony with the view that a Tm mechanism is involved and constant on any single occasion though it may change for unknown causes from day to day. Eight instances in which there was little or no correlation were believed to indicate inconstancy of filtration resulting from glomerular intermittency. It is impossible to rule out changes in tubular function, however, particularly in view of the relative instability of phosphate reabsorption under many circumstances.

Phosphate excretion increases markedly in response to an acid load or acidification of the urine. This response does not necessarily imply that phosphate Tm has decreased since the relation between filtered load and transfer may be affected independently of the maximal capacity. Thus acidosis produced by hydrochloric acid infusion does not affect Tm whereas acidosis following intravenous administration of Diamox lowers it (206).

Phosphate appears to share at least in part the same system by which glucose is reabsorbed since a glucose load depresses phosphate Tm. Phlorizin reverses this effect and actually increases Tm above the control value (207). It may be surmised that other substances occurring naturally in the blood also interfere with transfer and account in part for the variability noted by Longson *et al.* (112) and other workers (208). The vital importance of phosphate in the body's metabolic economy undoubtedly also exposes the transfer mechanism to the influence of additional unknown factors of even greater significance.

Sulfate.—Sulfate excretion may be related to phosphate excretion since both are similarly affected by glucose and phlorizin (207), but the interrelations between the two have not been thoroughly explored. Sulfate is reabsorbed by a limited transfer system which, unlike that for phosphate, is saturated only at relatively high plasma concentrations. Little is known about stability or reproducibility of sulfate Tm. Recent studies (209, 210) indicate that it varies with filtration rate in the dog, in this also resembling phosphate, but unlike phosphate, is depressed following administration of sodium chloride. Amino acids seem to interfere with the transfer of sulfate in proportion to their maximal transfer rates (210), possibly as a result of competitive inhibition though it is not certain that sulfate depresses amino acid transport. These findings are in accord with observations of Deyrup (211) that accumulation of S^{35}-sulfate in rat renal tissue slices was enhanced by phlorizin and reduced by inhibitors of oxidative phosphorylation. Hunt

(212) has brought forward evidence that the dietary intake of sulfate rather than phosphate appears to determine urinary pH.

Regulation of Electrolyte Excretion

Electrolyte excretion is closely tied in with body needs. To some extent, as noted above, output is dictated by the character of the local milieu and the interrelationships between ions and other substances within the urine but at all times maintenance of a balance between intake and output, between tissue reservoirs and plasma pool, or between external and internal environment exert an overriding influence. Body weight, body composition, and the distribution of constituents within the body is kept within narrow bounds as a result of the renal adjustments to supply and to stress. Although local factors affecting transfer are of considerable importance from moment to moment in determining urine formation, all adjustments in the long run are dictated by the requirements of the whole. These needs influence renal function indirectly through exciting the release of humoral agents that act directly upon tubular transfer systems. A number of these agents have been identified and much new information on their action has appeared during the past year. The kidney possesses an elaborate innervation by means of which tubular function may also be subject to control. Finally, the complete dependence of kidney function upon the circulation indicates the importance of hemodynamic adjustments in effecting far-reaching changes in electrolyte excretion.

Integration of the alterations produced by these different agencies is not understood, though it seems probable that any given situation involves a manifold reorganization geared to correct a variety of imbalances simultaneously. In this way any disorder of body fluid and composition elicits a multifaceted response that assures restoration to the "normal" state even if one or several response systems have been damaged. It must be stressed that the state to which the system tends to return is not always easy to define. In normal healthy animals, acute disequilibria are undoubtedly repaired by return to the control, but when an abnormal state is long maintained, new patterns may be established and a forced "return to normal" may prove harmful. The mechanisms by which various "sets" are determined remain wholly obscure. As a first approach to this vital problem, an understanding of the patterns of control and adjustment is necessary.

Humoral control.—The adrenal cortex is a well-recognized source of hormonal agents that exert a powerful influence upon renal tubular function. The most recently discovered of these, aldosterone, occurs naturally in adrenal venous blood, is detectable in body fluids by bio-assay or chromatographic methods as the 11,18-hemiacetal form of 18-aldehydocorticosterone, and is approximately 30 times more effective than deoxycorticosterone in changing tubular reabsorption of sodium and potassium (213 to 222). Studies of output in the adrenal venous blood of the dog indicate that aldosterone dominates the steroids released in terms of its effect upon electrolyte

excretion (220) though hydrocortisone may be present in larger absolute quantities in the peripheral blood of dog and man (213). Aldosterone secretion appears to persist following hypophysectomy in the dog (220, 223) though the matter is not yet settled (221). In any case, aldosterone appears to promote tubular sodium reabsorption and potassium secretion.

More or less constant secretion may have a "permissive" effect in providing the physiologic setting upon which a normal response is contingent, but the evidence suggests in addition that aldosterone secretion varies with need and that aldosterone may exert a direct and variable action of its own (213). The mechanisms which condition and control release are disputed but are probably multiple, varying in intensity and effectiveness with the situation. Leutscher & Curtis (215, 224) tend to stress the importance of the concentration and mass of sodium in the body fluids to which aldosterone output seems to be inversely related. Laragh & Stoerk (225) emphasize the influence of potassium because sodium depletion with the development of hyponatremia in the dog does not elicit aldosterone secretion unless potassium is given in the diet. Bartter (226) and other workers (227, 228) have been more impressed by the relationship between change in the volume of body fluids (particularly of the blood) and aldosterone activity in the urine independent of altered sodium and potassium availability. They suggest that the volume of some component of the body fluid or some function of volume (such as blood pressure level in a critical circuit) may be the decisive antecedent to release. Much has been made of the tendency for aldosterone excretion to be elevated in abnormal states of sodium retention but no clear-cut evidence of causal relationship has been forthcoming. A flourishing literature of speculation and conjecture regarding the role of aldosterone in various clinical conditions is springing up. Additional instances of aldosterone-producing tumors of the adrenal cortex giving rise to hypokaliemia, alkalosis, hypertension, muscle weakness, tetany, and polyuria have been reported (229 to 232).

Studies of the changes produced by adrenalectomy or disease of the adrenals yield more direct evidence on adrenal-renal interrelationships in the intact animal although the findings must ultimately be tested in terms of the effects of individual substances secreted by the adrenal cortex. Adrenalectomy results in a vasoconstrictive response in which filtration is reduced and which persists even during adequate deoxycorticosterone (DCA) therapy. Excessive hydration or cortisone therapy results in a rise in filtration, presumably in connection with other, as yet uncertain, circulatory responses. The defect in tubular reabsorption of sodium is corrected by DCA, aldosterone, and, to a much less obvious degree, by cortisone. The impaired diuretic response to water loading is restored by cortisone, but not by DCA. On the basis of careful study of discrete renal functions of two dogs before and after adrenalectomy Garrod, Davies & Cahill (142) believe that this effect of cortisone does not depend upon increased filtration. In one of their dogs,

peak urine flows were not correlated with glomerular filtration rates during cortisone therapy; in the second a positive correlation was apparent. Sodium excretion in the untreated adrenalectomized animal appears to be closely related to filtration rate (142, 233). Diminished filtration does not prevent the loss of an excessive amount of sodium in the urine on low or normal sodium intake, but it does seem to interfere with satisfactory elimination of sodium loads (233). Hence adrenal insufficiency is characterized by a tendency both to lose and to retain sodium. Adrenalectomized human subjects behave similarly (234). Potassium retention is as consistent, but not as dramatic in its effect, as sodium loss after adrenalectomy. DCA, cortisone, and aldosterone are all effective in promoting potassium output—even to excess. Sodium loss seems to be associated as a rule with chloride but more careful study of cation-anion relationship should be made. Giebisch, MacLeod & Pitts (235) report that the increased bicarbonate reabsorption with DCA administration in normal dogs is apparently attributable to potassium depletion and not to a specific effect of the steroid. The site of action of the cortical hormones remains disputed though it seems likely that mechanisms within the cells of the renal tubule are affected directly. Shifts in fluid and electrolytes that are impossible to explain on the basis of renal effects suggest that other tissue cells are also affected (236, 237). Hartroft & Hartroft (238) describe the development of granulation in the cells of the juxtaglomerular aparatus in the rat during salt restriction that is positively correlated in degree with width of the zona glomerulosa of the adrenal cortex. These structures, which are not as prominent in other animal species, are intimately related both to vascular and tubular cells.

The adrenal medulla secretes epinephrine and norepinephrine in response to a variety of stimuli (53). Both agents appear to have a direct effect upon both the vasculature and parenchyma of the kidney (42, 53, 239). Renal functional responses are notably variable, depending upon dose, species, and physiologic setting, i.e., anesthesia, apprehension, hydration, electrolyte load, and the like. Blake (42, 239, 240) has adduced evidence in support of the view that epinephrine has two separate actions: "direct," possibly involving intrarenal vascular adjustment and tending to reduce sodium excretion, and "indirect," attributable (*a*) to elevation of blood pressure and stimulation of the carotid sinus with resultant increased output of salt and water and (*b*) to action upon some cerebral or medullary "center" that produces a delayed reduction in water and electrolyte excretion. The data presented (42, 239, 240) demonstrate the apparently erratic effects of the medullary amines. These substances undoubtedly produce significant alterations in renal function and play an important role in changing urine formation in various situations. Unfortunately, the interactions between the neural and chemical effects are so intimately related that analysis of action is exceedingly difficult. In addition, it is quite possible that adrenal cortical activity is influenced by epinephrine and norepinephrine since the excretions of 17-

ketosteroids and epinephrine are positively correlated and epinephrine appears to accelerate cortical secretion by releasing ACTH in many animals (241, 242).

Further studies are needed to define the role of the adrenal cortex and medulla in the pathogenesis of so-called diurnal rhythms in electrolyte and water excretion. Doe, Flink & Goodsell (243) do not agree with the view of earlier workers that cyclic changes in renal tubular activity affect intracellular pH with resultant shifts of potassium but believe rather that a diurnal variation in adrenal cortical activity, evident in variation in 17-hydroxycorticosteroid levels in blood and urine, may be responsible. Goldman & Luchsinger (244) were unable to detect rhythmic changes in ADH that might account for the phenomenon. A physicochemical explanation for rhythmic water and salt exchanges across the membrane of marine eggs may have relevance in this connection [Teorell (245)]. Though concerned with relatively rapid fluctuations, Teorell's hypothesis of a "hydrodynamical—electrical feed-back" resulting from imbalances between fluid and ionic movements along electropotential and chemical gradients may be applicable to longer periods.

The parathyroid elaborates a hormone that acts directly upon both bone and renal tubule cells. Foulks (246) has recently reported that intramuscular injection of a single dose of parathyroid extract is not adequate to induce the immediate development of phosphaturia in dogs but requires preliminary "priming doses" or prolonged intravenous administrations. The requisite latent period and rapid inactivation may account for failure of many investigators to confirm earlier work demonstrating phosphaturia. Diminished phosphate reabsorption appears to be attributable to a change in the transfer mechanism (208). However, neither the reduction in transfer during phosphate administration nor the increase during infusion of calcium gluconate can be attributed to an increment or decrement, respectively, in hormone release because the renal effect of parathyroid hormone is not sufficiently rapid according to Foulks (246). In addition to the seemingly direct action upon the renal tubular cells, parathyroid hormone also induces changes in the renal vasculature and glomerular filtration that may be involved in altering phosphate excretion.

Estrogens also seem to exert a direct action upon the renal tubules in promoting electrolyte retention. Preedy & Aitken (247) and Dignam, Voskian & Assali (248) report that repeated intramuscular injections of estradiol produced a significant reduction in the daily excretion of sodium and chloride in the absence of changes in glomerular filtration and renal blood flow. Output of potassium or phosphate is not altered significantly. Preedy & Aitken (247) also found that urine flow decreased significantly in association with a tendency to gain weight. Rapid degradation of the hormone by the liver (249, 250) probably accounts for its apparent inactivity when administered by the intravenous route (248).

Neural control.—The role of the nervous system in the regulation of

electrolyte and water excretion remains unsettled and controversial. Injury to the brainstem apparently evokes an increase in electrolyte excretion (251). Denervation of the kidney also results in increased excretion of sodium, osmotically active solutes, water, and creatinine for a period of several days to two weeks (44, 45). Sartorius & Burlington (44) connected the left renal artery and vein in one dog to the carotid artery and jugular vein of a second animal in such a manner that the renal perfusion pressure could be changed simply by raising or lowering the donor animal relative to the recipient. In this preparation, sodium and urine output were higher at any pressure level after denervation than before. Potassium output was not greatly affected though the sum of sodium and potassium concentrations tended to be constant after denervation. The urinary sodium concentration always rose though total osmolar concentration tended to fall (45). Hence, diminished sodium reabsorption appears to be the most important immediate effect of denervation, with a rise in urine flow as secondary phenomenon. Sartorius & Burlington (44) suggest that the renal nerves have a direct influence upon renal tubular reabsorptive capacity. It is difficult to assess the nonspecific role of trauma and anesthesia and to provide adequate controls in experiments of this kind. A difference in function is clearly apparent but whether it may be attributed to tubular rather than a local circulatory change cannot be decided on the evidence. Certainly the difference between kidneys following unilateral denervation tends to vanish with time and then, as Surtshin & Schmandt (45) point out, "any effect of the renal nerves upon the excretion of sodium in the untraumatized, unanesthetized, dog is small in comparison to other factors, known or unknown, acting on the kidneys." The denervated or transplanted kidney responds to water and salt loads in a normal manner (252 to 255). A fall in blood pressure following hemorrhage, on the other hand, elicits a much less striking reduction in urine flow and sodium excretion possibly because filtration is not as much affected as in the innervated kidney (43, 252). It is possible that other functions that depend upon intrarenal hemodynamic adjustments are also impaired (255) but more work is needed to confirm the scanty evidence now available.

Although transplantation appears to assure denervation, it may introduce other factors that alter function independently of the interruption of the nerve supply. Changes may occur very quickly in both auto- and homotransplants (256, 257) if proper precautions are not taken to assure a continued and ample blood supply, to prevent anesthetic vasoconstriction, and to avoid undue manipulation. The problem of homotransplantation has received much attention lately in the hope of finding a more satisfactory method of treating uremia in man. Renal homografts have proved disheartenningly short-lived in animals and in man. Urine formation begins almost immediately after transfer, persists for a few days, and then ceases abruptly. The graft disintegrates and is resorbed. The relative rapidity with which these changes develop cast doubt upon data obtained in studies of the trans-

planted kidney. However, Bricker *et al.* (255) have recently reported "reversal of the manifestations of uremia and malignant hypertension" in a man whose kidneys were replaced by a normal kidney taken from his healthy monozygotic twin brother. Survival of the patient in good health to the present, more than one year after the transplantation, almost warrants the authors' claim to a "successful transplantation." The cause for the development of anuria in the homotransplanted kidney before there is much structural change is believed by Darmady, Dempster, & Stranack (258) to lie in a progressive narrowing of the "glomerular tubular neck" which is demonstrable on microdissection. It is generally believed that rejection of the homograft is the result of immune reactions in the host that may be susceptible to control. Kamrin & Kamrin (259, 260) have found that the grafted renal tissue remains viable, though not functioning normally, in parabiotic rats even after the parabionts have been separated. Similarly, Egdahl & Hume (261) report that continuous cross-perfusion of two dogs following transplantation stabilizes the graft in some manner so that rejection is delayed or inhibited. In the light of these developments, some hope may be held out for the ultimate development of satisfactory methods of transfer. The data already available give weight to the view that renal innervation is not necessary for normal urine formation though possibly of importance in facilitating or initiating certain adjustments.

Circulatory control.—In theory, hemodynamic adjustments could preponderate in the control of changes in electrolyte excretion. With the exception of potassium and hydrogen ion, the urinary electrolyte passes into the tubular fluid almost entirely by filtration alone. Since reabsorption at any point in the tubule must depend to a large extent upon the volume and composition of the residual filtrate presented for processing, appropriate changes in filtration by vascular adjustment could easily account for large alterations in urine flow and content. In fact, however, the effects of adrenalectomy or hypophysectomy demonstrate convincingly the usual dominance of tubular function in the control of electrolyte and water excretion. Changes in filtration seem to assume a greater importance in man and dog in situations of extreme stress, such as hemorrhage or hypothermia. In certain species such as the seal (6) large swings in filtration rate and renal blood flow clearly do govern urine formation under most circumstances, and it is probable that small undetectable shifts may be of moment under less extreme conditions in other animals. The difficulty of evaluating these possibilities lies, first, in the lack of knowledge regarding the effects of hemodynamic factors alone, uncomplicated by tubular functional responses other than those induced by the circulatory change. Second, there are uncertainties regarding the precise local implication of hemodynamic rearrangements. Third, detection is difficult. Tentative efforts have been made to grapple with these questions in the past year, though little has been accomplished apart from somewhat clearer definition.

There is certain similarity in the pattern of electrolyte excretion during

circulatory responses. The upright position (156, 262), exercise (73), elevated abdominal pressure (76, 77, 78), the action of depressor drugs (46, 47, 48, 81), hemorrhage (43, 263), hypothermia (63, 64, 264), heat stress (265) and interference with renal perfusion (266) all diminish filtration and provoke a more marked reduction in sodium excretion than in urine flow and a greater fall in both than in filtration. Potassium excretion appears to follow filtration rather closely or actually increases. It is extremely difficult to rule out extrarenal influences upon tubular function in the development of these responses. Indeed, denervation (43), adrenalectomy (263), and suppression of posterior pituitary activity (76) appear to have a modifying effect; but the fact that tubular function may vary in relation to filtration alone seems well-founded. Although increased reabsorption of water and sodium with diminished filtration seems reasonably certain, it is not known if potassium or hydrogen ion secretion is enhanced, how anion transport is affected, or what an elevation in filtration would do.

The mechanism by which a change in filtration is reflected in altered urine formation remains obscure; (*a*), uniform elevation or depression in filtration rate could affect the velocity of filtrate movement through the tubule and in so doing decrease or shorten the time of contact between cells and filtrate during which transfers are effected, (*b*), filtration might be affected nonuniformly with cessation of filtrate formation in some glomeruli and no change in others. If nephrons differ in functional capacity, altered urinary composition could result from a rearrangement in the population of nephrons currently contributing to urine formation rather than from actual changes in movements of solute or water across the nephron wall. Third, circulatory readjustment could give rise to localized changes in pressure, volume or flow that could affect nephrons directly and in a limited manner. Thus a rise in pressure in the medulla could conceivably act chiefly upon the thin segment and affect urine formation only insofar as local segmental operation is concerned. Exploration of these possibilities has scarcely begun but what work has been reported suggests that interesting developments may be anticipated. It seems likely that all are implicated, uniform change in filtration playing a major role (118, 119, 266) with nephron populational shifts having a definite though lesser influence (76, 112, 266). Similar patterns of electrolyte excretion during hypoxia or hypercapnia suggest that localized circulatory change could have a direct effect on tubular function by changing the delivery or removal of metabolites though it is possible that these responses depend upon central neural (or humoral) mediation (267, 268). Perhaps factors of this kind may be involved in the tendency for sodium chloride and potassium output to increase more rapidly and to a more marked degree during infusion of 2.5 per cent sodium chloride solution in hypertensive than in normotensive subjects (269).

The recognition and detection of physiologically significant adjustments in the intrarenal circulation and glomerular filtration present a major problem. The effect of even large changes can be masked by simultaneous tubular

and hemodynamic compensations. For example, in 6 dogs subjected to partial occlusion of one renal artery with resultant unilateral anuria, Surtshin & Latorre (270) found that removal of the unmolested opposite kidney was followed by restoration of function or even an increase in function in the remaining, previously anuric, kidney without change in the degree of constriction. On the other hand, the methods available for measuring filtration and blood flow are probably too crude to permit detection of small but important changes such as those that occur following closure of an arteriovenous fistula (74) or that may modify the action of adrenal medullary amines (241). Improved methods are urgently required to permit further exploration of these questions.

LITERATURE CITED

1. Schachter, D., *Med. Clin. N. Amer.*, **39**, 681–98 (1955)
2. Winton, F. R., *Ann. Rev. Physiol.*, **18**, 225–52 (1956)
3. Bradley, S. E., *Actualités Biologiques*, **2**, 63–105 (1955)
4. Holley, H. L., and Carlson, W. W., *Potassium Metabolism in Health and Disease* (Charles C Thomas, Springfield, Ill., 131 pp., 1955)
5. Edwards, J. G., *J. Urol.*, **75**, 200–08 (1956)
6. Elkinton, J. R., and Danowski, T. S., *The Body Fluids, Basic Physiology and Practical Therapeutics* (The Williams and Wilkins Company, Baltimore, Md., 626 pp., 1955)
7. Welt, L. G., *Clinical Disorders of Hydration and Acid-Base Equilibrium* (Little, Brown and Co., Boston, Mass., 262 pp., 1955)
8. Smith, H. W., *Principles of Renal Physiology* (Oxford University Press, New York, N. Y., 237 pp., 1956)
9. Pease, D. C., *Anat. Record*, **121**, 701–22 (1955)
10. Pease, D. C., *Anat. Record*, **121**, 723–44 (1955)
11. Pease, D. C., *J. Histochem. Cytochem.*, **3**, 295–308 (1955)
12. Piel, C. F., Dong, L., Modern, F. W. S., Goodman, J. R., and Moore, R., *J. Exptl. Med.*, **102**, 573–80 (1955)
13. Darmady, E. M., and Stranack, F., *Proc. Roy. Soc. Med.*, **48**, 781–83 (1955)
14. Gormsen, H., Iversen, P., and Raaschoy, F., *Am. J. Med.*, **19**, 209–21 (1955)
15. Muehrcke, R. C., Pirani, C. L., Pollack, V. E., and Kark, R. M., *Guy's Hosp. Repts.*, **104**, 295–311 (1955)
16. Muehrcke, R. C., Kark, R. M., and Pirani, C. L., *J. Urol.*, **74**, 267–77 (1955)
17. Schwiebinger, G. W., and Hodges, C. V., *J. Am. Med. Assoc.*, **159**, 1198–1201 (1955)
18. Nedeljković, R., *arch. Intern. physiol.*, **64**, 34–45 (1956)
19. Nedeljković, R., *arch. Intern. physiol.*, **64**, 46–64 (1956)
20. Chinard, F. P., *Am. J. Physiol.*, **185**, 413–17 (1956)
21. Sapirstein, L. A., Vidt, D. G., Mandel, M. J., and Hanusek, G., *Am. J. Physiol.*, **181**, 330–36 (1955)
22. Mandel, M. J., Vidt, D. G., and Sapirstein, L. A., *Am. J. Physiol.*, **182**, 428–32 (1955)
23. Mériel, P., Galinier, F., Ribaut, S., and Suc, J. -M., *Hémodynamique rénale* (G. Doin et Cie, Paris, France, 159 pp., 1956)

24. Brun, C., Crone, C., Davidsen, H. G., Fabricius, J., Tybjaerg Hansen, A., Lassen, N. A., and Munck, O., *Proc. Soc. Exptl. Biol. Med.*, **89**, 687–90 (1955)
25. Green, I., *Federation Proc.*, **15**, 81 (1956)
26. Lilienfeld, L. S., Porfido, F. A., and Rose, J. C., *J. Clin. Invest.*, **35**, 721–22 (1956)
27. Wheeler, H. O., Combes, B., Childs, A. W., and Wade, O. L., *Trans. Assoc. Am. Physic.*, **68**, 177–84 (1955)
28. Brun, C., Crone, C., Davidsen, H. G., Fabricius, J., Tybjaerg Hansen, A., Lassen, N. A., and Munck, O., *Proc. Soc. Exptl. Biol. Med.*, **91**, 199–202 (1956)
29. de Wardener, H. D., *Lancet*, **1**, 580–84 (1955)
30. Reubi, F., *Experientia*, **12**, 33–34 (1956)
31. Weaver, A. N., McCarver, C. T., and Swann, H. G., *J. Exptl. Med.*, **104**, 41–52 (1956)
32. Gottschalk, C. W., and Mylle, M., *Am. J. Physiol.*, **185**, 430–39 (1956)
33. Pappenheimer, J. R., and Kinter, W. B., *Am. J. Physiol.*, **185**, 377–90 (1956)
34. Schück, O., and Chytil, M., *Physiol. Bohemoslov.*, **5**, 103–10 (1956)
35. Piiper, J., and Schürmeyer, E., *Pflügers Arch. ges. Physiol.*, **261**, 543–49 (1955)
36. Kinter, W. B., and Pappenheimer, J. R., *Am. J. Physiol.*, **185**, 391–98 (1956)
37. Barnett, C. H., and Cochrane, W., *Nature*, **177**, 740–42 (1956)
38. Schieve, J. F., *J. Lab. Clin. Med.*, **46**, 948–49 (1955)
39. Malizia, E., *Acta Med. Scand.*, **154**, 399–406 (1956)
40. Kinter, W. B., and Pappenheimer, J. R., *Am. J. Physiol.*, **185**, 399–406 (1956)
41. Swann, H. G., Valdivia, L., Ormsby, A. A., and Witt, W. T., *J. Exptl. Med.*, **104**, 25–40 (1956)
42. Blake, W. D., *Am. J. Physiol.*, **181**, 399–416 (1955)
43. Bálint, P., Fekete, A., and Szalay, S., *Experientia*, **12**, 228–29 (1956)
44. Sartorius, O. W., and Burlington, H., *Am. J. Physiol.*, **185**, 407–12 (1956)
45. Surtshin, A., and Schmandt, W. P., *Am. J. Physiol.*, **185**, 418–25 (1956)
46. Rønnov-Jesson, V., *Scand. J. Clin. Lab. Invest.*, **7**, 160–66 (1955)
47. Moyer, J. H., and Hershberger, R. L., *Am. J. Med. Sci.*, **231**, 294–312 (1956)
48. Stover, J. W., Griffin, R. W., and Ford, R. V., *Ann. Internal. Med.*, **44**, 893–98 (1956)
49. Brull, L., Louis-Bar, D., and Lybeck, H., *Acta Physiol. Scand.*, **34**, 175–82 (1955)
50. Bálint, P., Fekete, Á., Hajdu, A., and Kiss, É., *Acta Med. Scand.*, **154**, 407–15 (1956)
51. Haddy, F. J., *Federation Proc.*, **15**, 85–86 (1956)
52. Friedman, S. M., Radcliffe, R. W., Turpin, J. E. H., and Friedman, C. L., *Can. J. Biochem. Physiol.*, **34**, 158–69 (1956)
53. von Euler, U. S., *Noradrenaline—Chemistry, Physiology, Pharmacology, and Clinical Aspects* (Charles C Thomas, Springfield, Ill., 382 pp., 1956)
54. Watts, D. T., *J. Pharmacol. Exptl. Therap.*, **114**, 203–210 (1955)
55. Murdaugh, H. V., Jr., *J. Lab. Clin. Med.*, **48**, 69–75 (1956)
56. Sudin, T., *Acta Med. Scand.*, **154**, Suppl. 313, 1–57 (1956)
57. Little, J. M., Kelsey, W. M., and Yount, E. H., Jr., *Am. J. Physiol.*, **185**, 759–66 (1956)
58. Wakerlin, G. E., *Physiol. Revs.*, **35**, 555–82 (1955)
59. Kolff, W. J., and Page, I. H., *Am. J. Physiol.*, **181**, 575–79 (1955)

60. Handler, P., *Am. J. Physiol.*, **184,** 400–05 (1956)
61. Vanatta, J. C., Danhof, I., and McMullen, M., *Am. J. Physiol.*, **185,** 167–70 (1956)
62. Bresler, E. H., *Am. J. Med. Sci.*, **232,** 93–104 (1956)
63. Page, L. B., *Am. J. Physiol.*, **181,** 171–78 (1955)
64. Hong, S. K., *Am. J. Physiol.*, **183,** 628 (1955)
65. Andersen, M., and Nielsen, K. C., *Acta Med. Scand.*, **151,** 191–99 (1955)
66. Brod, J., Fencl, V., Gerová, M., Hejl, Z., Jirka, J., Kotanová, E., Prát, V., and Zajíc, F., *Acta Med. Scand.*, **154,** Suppl. 312, 242–45 (1956)
67. Egdahl, R. H., and Richards, J. B., *Am. J. Physiol.*, **185,** 239–42 (1956)
68. Knocker, P., *Lancet*, **2,** 837–40 (1955)
69. Burwell, R. G., *J. Pathol. Bacteriol.*, **70,** 387–99 (1955)
70. Henry, J. P., *Wright Air Development Center (WADC) Tech. Rep.*, 55–478, 1–103 (1956)
71. Henry, J. P., Gauer, O. H., and Reeves, J. L., *Circulation Research*, **4,** 85–90 (1956)
72. Watts, D. T., *Am. J. Physiol.*, **184,** 271–74 (1956)
73. Freeman, O. W., Mitchell, G. W., Wilson, J. S., Fitzhugh, F. W., and Merrill, A. J., *J. Clin. Invest.*, **34,** 1109–13 (1955)
74. Hilton, J. G., Kanter, D. M., Hays, D. R., Bowen, E. H., Golub, J. R., Keating, J. H., and Wégria, R., *J. Clin. Invest.*, **34,** 732–36 (1955)
75. Forster, R. P., and Nyboer, J., *Am. J. Physiol.*, **183,** 149–54 (1955)
76. Bradley, S. E., Mudge, G. H., Blake, W. D., and Alphonse, P., *Acta clin. belg.*, **10,** 209–23 (1955)
77. Pritchard, J. A., Barnes, A. C., and Bright, R. H., *J. Clin. Invest.*, **34,** 777–81 (1955)
78. Hendricks, C. H., and Barnes, A. C., *Am. J. Obstet. Gynecol.*, **69,** 1225–32 (1955)
79. Bradley, S. E., and Anderson, D. L., *Bull. Sch. Med. Univ. of Md.*, **41,** 39–45 (1956)
80. Ramsay, A. G., Derrick, J. B., Lewis, J. A., and Stevenson, J. A. F., *Can. Med. Assoc. J.*, **72,** 356–62 (1955)
81. Krogsgaard, A. R., *Acta Med. Scand.*, **154,** 41–51 (1956)
82. Damaria, W. J. A., and Harris, J. S., *Am. J. Physiol.*, **182,** 251–55 (1955)
83. Etteldorf, J. N., Smith, J. D., Tharp, C. P., and Tuttle, A. H., *Am. J. Diseases Children*, **89,** 451–62 (1955)
84. Oliver, J., *Livre Jubilaire publié en l'honneur du Professeur Paul Govaerts* 1–12 (Imprimerie medicale et scientifique, Brussels, Belgium, 756 pp., 1955)
85. Walser, M., Davidson, D. G., and Orloff, J., *J. Clin. Invest.*, **34,** 1520–23 (1955)
86. Barnard, H. F., Bassir, O., and Hough, J. M., *Quart. J. Exptl. Physiol.*, **40,** 217–24 (1955)
87. Deane, N., and Smith, H. W., *J. Clin. Invest.*, **34,** 681–84 (1955)
88. Ladd, M., Liddle, L., and Gagnon, J. A., *Am. J. Physiol.*, **184,** 505–14 (1956)
89. Swanson, R. E., *Am. J. Physiol.*, **184,** 527–34 (1956)
90. Gribetz, D., Van Loon, K., and Crawford, J. D., *Am. J. Physiol.*, **183,** 401–05 (1955)
91. Chinard, F. P., Vosburgh, G. J., and Enns, T., *Am. J. Physiol.*, **183,** 221–34 (1955)
92. Garby, L., *Acta Physiol. Scand.*, **35,** 88–92 (1955)

93. McGarry, E., Sehon, A. H., and Rose, B., *J. Clin. Invest.*, **34**, 832–44 (1955)
94. Boyce, W. H., and Swanson, M., *J. Clin. Invest.*, **34**, 1581–89 (1955)
95. Porter, K. R., and Tamm, I., *J. Biol. Chem.*, **212**, 135–40 (1955)
96. Fister, G. M., and Cochran, G. W., *J. Urol.*, **74**, 828–39 (1955)
97. Fowweather, F. S., *Brit. Med. J.*, **2**, 1419–23 (1955)
98. Malmendier, Cl., and Lambert, P. -P., *J. d'Urol.*, **61**, 327–32 (1955)
99. Straus, W., and Oliver, J., *J. Exptl. Med.*, **102**, 1–9 (1955)
100. Logothetopoulos, J., and Weinbren, K., *Brit. J. Exptl. Path.*, **36**, 402–06 (1955)
101. Finlayson, J. S., and Baumann, C. A., *Am. J. Physiol.*, **184**, 469–72 (1956)
102. Rumsfeld, H. W., Jr., *Am. J. Physiol.*, **184**, 473–78 (1956)
103. Sellers, A. L., and Marmorston, J., *Am. J. Physiol.*, **183**, 299–301 (1955)
104. Sellers, A. L., Roberts, S., Rask, I., and Marmorston, J., *Am. J. Physiol.*, **183**, 406–12 (1955)
105. Coye, R. D., Jr., Maude, D. L., Dibble, R. F., and Yuile, C. L., *Arch. Path.*, **60**, 548–55 (1955)
106. Wégria, R., Capeci, N. E., Blumenthal, M. R., Kornfeld, P., Hays, D. R., Elias, R. A., and Hilton, J. G., *J. Clin. Invest.*, **34**, 737–43 (1955)
107. Lathem, W., and Benjamin, A. D., *J. Clin. Invest.*, **38**, 719–20 (1956)
108. Löwgren, E., *Acta Med. Scand.*, **151**, Suppl. 300, 1–52 (1955)
109. Childs, A. W., Wheeler, H. O., Cominsky, B., Leifer, E., Wade, O. L., and Bradley, S. E., *J. Clin. Invest.*, **34**, 926 (1955)
110. Chinard, F. P., and Enns, T., *Am. J. Physiol.*, **182**, 247–50 (1955)
111. Dempster, W. J., Eggleton, M. G., and Shuster, S., *J. Physiol.*, **132**, 213–24 (1956)
112. Longson, D., Mills, J. N., Thomas, S., and Yates, P. A., *J. Physiol.*, **131**, 555–71 (1956)
113. Grossman, J., Weston, R. E., Borun, E. R., and Leiter, L., *J. Clin. Invest.*, **34**, 1611–24 (1955)
114. de Wardener, H. E., and del Greco, F., *Clin. Sci.*, **14**, 715–23 (1955)
115. Welt, L. G., *Metabolism, Clin. and Exptl.*, **5**, 395–403 (1956)
116. Swanson, R. E., Hoshiko, T., and Visscher, M. B., *Am. J. Physiol.*, **184**, 535–41 (1956)
117. Ussing, H. H., and Andersen, B., *Proc. Third International Congress of Biochemistry* (Brussels 1955), 434–40 (Academic Press, New York, N. Y., 544 pp., 1956)
118. del Greco, F., and de Wardener, H. E., *J. Physiol.*, **131**, 307–16 (1956)
119. Berliner, R. W., and Davidson, D. G., *J. Clin. Invest.*, **35**, 690 (1956)
120. Kleeman, C. R., Epstein, F. H., and White, C., *J. Clin. Invest.*, **35**, 749–56 (1956)
121. Baldwin, D. S., Berman, H. J., Heinemann, H. O., and Smith, H. W., *J. Clin. Invest.*, **34**, 800–07 (1955)
122. Ikkos, D., Luft, R., and Olivecrona, H., *J. Clin. Endocrinol. Metab.*, **15**, 553–67 (1955)
123. Lipsett, M. B., MacLean, J. P., West, C. D., Li, M. C., and Pearson, O. H., *J. Clin. Endocrinol. and Metabolism*, **16**, 183–95 (1956)
124. Macdonald, W. B., *Pediatrics*, **15**, 298–311 (1955)
125. West, J. R., and Kramer, J. G., *Pediatrics*, **15**, 424–32 (1955)
126. Flax, L. J., and Gersh, I., *Am. J. Diseases Children*, **89**, 602–05 (1955)

127. Cannon, J. F., *Arch. Internal Med.*, **96**, 215–72 (1955)
128. Levinger, E. L., and Escamilla, R. F., *J. Clin. Endocrinol. and Metabolism*, **15**, 547–52 (1955)
129. Moehlig, R. C., and Schultz, R. C., *J. Am. Med. Assoc.*, **158**, 725–27 (1955)
130. van Dyke, H. B., Adamsons, K., Jr., and Engel, S. L., *Recent Progr. Hormone Research*, **11**, 1–41 (1955)
131. Green, J. D., and Van Breeman, V. L., *Am. J. Anat.*, **97**, 177–227 (1955)
132. Rennels, E. G., and Drager, G. A., *Anat. Record*, **122**, 193–203 (1955)
133. Harris, G. W., *Bull. Johns Hopkins Hosp.*, **97**, 358–75 (1955)
134. Bartlett, M. F., Jöhl, A., Roeske, R., Stedman, R. J., Stewart, F. H. C., Ward, D. N., and du Vigneaud, V., *J. Am. Chem. Soc.*, **78**, 2905–06 (1956)
135. van Dyke, H. B., Engel, S. L., and Adamsons, K., Jr., *Proc. Soc. Exptl. Biol. Med.*, **91**, 484–86 (1956)
136. Anslow, W. P., Jr., and Wesson, L. G., Jr., *Am. J. Physiol.*, **182**, 561–66 (1955)
137. Friedman, S. M., Nakashima, M., and Friedman, C. L., *Am. J. Physiol.*, **184**, 104–08 (1956)
138. Swingle, W. W., Brannick, L. J., Barrett, W., LeBrie, S. J., and Parlow, A. F., *Proc. Soc. Exptl. Biol. Med.*, **91**, 223–26 (1956)
139. West, C. D., Traeger, J., and Kaplan, S. A., *J. Clin. Invest.*, **34**, 887–98 (1955)
140. Crawford, J. D., and Pinkham, B., *J. Pharmacol. Exptl. Therap.*, **113**, 431–38 (1955)
141. Skillern, P. G., Corcoran, A. C., and Scherbel, A. L., *J. Clin. Endocrinol. and Metabolism*, **16**, 171–82 (1956)
142. Garrod, O., Davies, S. A., and Cahill, G., Jr., *J. Clin. Invest.*, **34**, 761–76 (1955)
143. Wagner, H. N., Jr., and Braunwald, E., *J. Clin. Invest.*, **35**, 742 (1956)
144. Hollander, W., Jr., Winters, R. W., Williams, T. F., Holliday, M., Oliver, J., and Welt, L. G., *J. Clin. Invest.*, **35**, 713 (1956)
145. Craig, J. M., and Schwartz, R., *Federation Proc.*, **15**, 513 (1956)
146. Siebenmann, R. E., *Schweiz. med. Wochschr.*, **85**, 468–71 (1955)
147. Relman, A. S., and Schwartz, W. B., *New Eng. J. Med.*, **255**, 195–203 (1956)
148. Jacobson, H. N., and Kellogg, R. H., *Am. J. Physiol.*, **184**, 376–89 (1956)
149. Shanes, A. M., Ed., *Electrolytes in Biological Systems* (American Physiological Society, Washington, D. C., 243 pp., 1955)
150. Giebisch, G., *Am. J. Physiol.*, **185**, 171–74 (1956)
151. Krakusin, J. S., and Jennings, R. B., *Arch. Path.*, **59**, 471–86 (1955)
152. Hoshiko, T., Swanson, R. E., and Visscher, M. B., *Am. J. Physiol.*, **184**, 542–47 (1956)
153. Schwartz, W. B., Jenson, R. L., and Relman, A. S., *J. Clin. Invest.*, **34**, 673–80 (1955)
154. Fuller, G. R., MacLeod, M. B., and Pitts, R. F., *Am. J. Physiol.*, **182**, 111–18 (1955)
155. Clarke, E., Evans, B., MacIntyre, I., and Milne, M. D., *Clin. Sci.*, **14**, 421–40 (1955)
156. Epstein, F. H., Kleeman, C. R., Lamdin, E., and Rubini, M. E., *J. Clin. Invest.*, **35**, 308–13 (1956)
157. Roberts, K. E., Randall, H. T., Vanamee, P., and Poppell, J. W., *Metabolism, Clin. and Exptl.*, **5**, 404–18 (1956)
158. Hoshiko, T., *Am. J. Physiol.*, **185**, 545–48 (1956)

159. Thomas, C. A., Jr., *Science*, **123**, 60–61 (1956)
160. Huf, E. G., *Electrolytes in Biological Systems*, 205–38 (Shanes, A. M., Ed., American Physiological Society, Washington, D. C., 243 pp., 1955)
161. Roberts, K. E., Randall, H. T., Sanders, H. L., and Hood, M., *J. Clin. Invest.*, **34**, 666–72 (1955)
162. Fitzgerald, M. G., and Fourman, P., *Lancet*, **2**, 848–50 (1955)
163. Falbriard, A., Muller, A. F., and Engel, E., *Rev. franç.*, **1**, 29–38 (1956)
164. Schwartz, W. B., *New Engl. J. Med.*, **253**, 601–08 (1955)
165. Anderson, H. M., and Mudge, G. H., *J. Clin. Invest.*, **34**, 1691–97 (1955)
166. Holland, W. C., and Auditore, G. V., *Am. J. Physiol.*, **183**, 309–13 (1955)
167. Mudge, G. H., *Electrolytes in Biological Systems*, 112–22 (Shanes, A. M., Ed., American Physiological Society, Washington, D. C., 243 pp., 1955)
168. Greif, R. L., and Jacobs, G. S., *Federation Proc.*, **15**, 82 (1956)
169. Emery, E. W., Holmes, R., Davies, H. E. F., and Black, D. A. K., *Clin. Sci.*, **14**, 241–44 (1955)
170. Black, D. A. K., Davies, H. E. F., Emery, E. W., and Wade, E. G., *Clin. Sci.*, **15**, 277–83 (1956)
171. Orloff, J., and Davidson, D. G., *Federation Proc.*, **15**, 139 (1956)
172. Laake, H., *Acta Med. Scand.*, **155**, 27–36 (1956)
173. Hanley, T., and Platts, M. M., *J. Clin. Invest.*, **35**, 20–30 (1956)
174. Iacobellis, M., Muntwyler, E., and Griffin, G. E., *Am. J. Physiol.*, **183**, 395–400 (1955)
175. Muntwyler, E., Iacobellis, M., and Griffin, G. E., *Am. J. Physiol.*, **184**, 83–90 (1956)
176. Satran, R., Brodsky, W. A., Moxley, T. I., and Greathouse, R., *Am. J. Physiol.*, **183**, 658 (1955)
177. Roberts, K. E., Poppell, J. W., and Randall, H. T., *Federation Proc.*, **15**, 153–54 (1956)
178. Hodler, J., Heinemann, H. O., Fishman, A. P., and Smith, H. W., *Am. J. Physiol.*, **183**, 155–62 (1955)
179. Coulson, R. A., and Hernandez, T., *Proc. Soc. Exptl. Biol. Med.*, **88**, 682–87 (1955)
180. Williams, J. K., *Federation Proc.*, **15**, 200–01 (1956)
181. Orloff, J., and Berliner, R. W., *J. Clin. Invest.*, **35**, 223–35 (1956)
182. Leonard, E., and Orloff, J., *Am. J. Physiol.*, **182**, 131–38 (1955)
183. Richterich-van Baerle, R., Goldstein, L., and Dearborn, E. H., *Science*, **124**, 74 (1956)
184. Williamson, B. J., and Freeman, S., *Federation Proc.*, **15**, 201 (1956)
185. Levitt, M. F., Halpern, M. H., Sweet, A. Y., and Gribetz, D., *J. Clin. Invest.*, **35**, 720–21 (1956)
186. Prien, E. L., and Walker, B. S., *J. Urol.*, **74**, 440–46 (1955)
187. Harrison, H. E., and Harrison, H. C., *J. Clin. Invest.*, **34**, 1662–70 (1955)
188. Sager, R. H., and Spargo, B., *Metabolism, Clin. and Exptl.*, **4**, 519–30 (1955)
189. Brull, L., and Cuypers, Y., *J. Marine Biol. Assoc. United Kingdom*, **34**, 637–42 (1955)
190. Brull, L., and Cuypers, Y., *J. Marine Biol. Assoc. United Kingdom*, **34**, 217–22 (1955)
191. Forster, R. P., and Berglund, F., *J. Gen. Physiol.*, **39**, 349–59 (1956)

192. Lee, C. C., and Wolterink, L. F., *Am. J. Physiol.*, **183**, 173–77 (1955)
193. Lee, C. C., and Wolterink, L. F., *Am. J. Physiol.*, **183**, 167–72 (1955)
194. Whittam, R., *J. Physiol.*, **131**, 542–54 (1956)
195. Solomon, S., *Federation Proc.*, **15**, 174–75 (1956)
196. Hilton, J. G., Capeci, N. E., Kiss, G. T., Kruesi, O. R., Glaviano, V. V., and Węgria, R., *J. Clin. Invest.*, **35**, 481–87 (1956)
197. Mudge, G. H., and Hardin, B., *J. Clin. Invest.*, **35**, 155–63 (1956)
198. Gardier, R. W., and Woodbury, R. A., *J. Pharmacol. Exptl. Therap.*, **114**, 453–60 (1955)
199. Greif, R. L., Sullivan, W. J., Jacobs, G. S., and Pitts, R. F., *J. Clin. Invest.*, **35**, 38–43 (1956)
200. Borghgraef, R. R. M., and Pitts, R. F., *J. Clin. Invest.*, **35**, 31–37 (1956)
201. Aikawa, J. K., and Fitz, R. H., *J. Clin. Invest.*, **35**, 775–78 (1956)
202. Cafruny, E. J., Farah, A., and Di Stefano, H. S., *J. Pharmacol. Exptl. Therap.*, **115**, 390–401 (1955)
203. Schwartz, W. B., Porter, R., and Relman, A. S., *Federation Proc.*, **15**, 166 (1956)
204. Ochwadt, B. K., and Pitts, R. F., *Am. J. Physiol.*, **185**, 426–29 (1956)
205. Wesson, L. G., Jr., *Am. J. Physiol.*, **183**, 391–94 (1955)
206. Malvin, R. L., and Lotspeich, W. D., *Am. J. Physiol.*, **183**, 641 (1955)
207. Cohen, J. J., Berglund, F., and Lotspeich, E. D., *Am. J. Physiol.*, **184**, 91–96 (1956)
208. Thompson, D. D., *Federation Proc.*, **15**, 186–87 (1956)
209. Berglund, F., and Lotspeich, W. D., *Am. J. Physiol.*, **185**, 533–38 (1956)
210. Berglund, F., and Lotspeich, W. D., *Am. J. Physiol.*, **185**, 539–42 (1956)
211. Deyrup, I., *Am. J. Physiol.*, **183**, 609 (1955)
212. Hunt, J. N., *Clin. Sci.*, **15**, 119–34 (1956)
213. Simpson, S. A., and Tait, J. F., *Ciba Foundation Colloquia on Endocrinology-Human Adrenal Cortex*, **8**, 204–27 (1955)
214. Wettstein, A., Kahnt, F. W., and Neher, R., *Ciba Foundation Colloquia on Endocrinology-Human Adrenal Cortex*, **8**, 170–89 (1955)
215. Luetscher, J. A., Jr., and Curtis, R. H., *Federation Proc.*, **14**, 746–51 (1955)
216. Gaunt, R., Renzi, A. A., and Chart, J. J., *J. Clin. Endocrinol. and Metabolism*, **15**, 621–46 (1955)
217. Neher, R., and Wettstein, A., *J. Clin. Invest.*, **35**, 800–05 (1956)
218. Liddle, G. W., Cornfield, J., Casper, A. G. T., and Bartter, F. C., *J. Clin. Invest.*, **34**, 1410–16 (1955)
219. Venning, E. H., Singer, B., Carballeira, A., Dyrenfurth, I., Beck, J. C., and Giroud, C. P., *Ciba Foundation Colloquia Endocrinology-Human Adrenal Cortex*, **8**, 190–203 (1955)
220. Farrell, G. L., Rauschkolb, E. W., and Royce, P. C., *Am. J. Physiol.*, **182**, 269–72 (1955)
221. Gaunt, R., *Ciba Foundation Colloquia Endocrinology-Human Adrenal Cortex*, **8**, 228–40 (1955)
222. Mach, R. S., and Fabre, J., *Ciba Foundation Colloquia Endocrinology-Human Adrenal Cortex*, **8**, 361–81 (1955)
223. Rauschkolb, E. W., Farrell, G. L., and Koletsky, S., *Am. J. Physiol.*, **184**, 55–58 (1956)
224. Luetscher, J. A., Jr., and Curtis, R. H., *Ann. Internal Med.*, **43**, 658–66 (1955)

225. Laragh, J. H., and Stoerk, H. C., *J. Clin. Invest.*, **34**, 913 (1955)
226. Bartter, F. C., *Metabolism, Clin. and Exptl.*, **5**, 369–83 (1956)
227. Muller, A. F., Riondel, A. M., and Mach, R. S., *Lancet*, **I**, 831–32 (1956)
228. Farrell, G. L., Rosnagle, R. S., and Rauschkolb, E. W., *Federation Proc.*, **15**, 60–61 (1956)
229. Foye, L. V., Jr., and Feichtmeir, T. V., *Am. J. Med.*, **19**, 966–75 (1955)
230. Mader, I. J., and Iseri, L. T., *Am. J. Med.*, **19**, 976–88 (1955)
231. Dustan, H. P., Corcoran, A. C., and Farrell, G. L., *J. Lab. Clin. Med.*, **46**, 809–10 (1955)
232. Chalmers, T. M., FitzGerald, M. G., James, A. H., and Scarborough, H., *Lancet*, **I**, 127–32 (1956)
233. Share, L., and Hall, P. W., 3rd., *Am. J. Physiol.*, **183**, 291–98 (1955)
234. Mendelsohn, M. L., and Pearson, O. H., *J. Clin. Endocrinol. and Metabolism*, **15**, 409–23 (1955)
235. Giebisch, G., MacLeod, M. B., and Pitts, R. F., *Am. J. Physiol.*, **183**, 377–86 (1955)
236. Cheek, D. B., and West, C. D., *Am. J. Physiol.*, **184**, 69–79 (1956)
237. Hare, K., and Hare, R. S., *Federation Proc.*, **15**, 87 (1956)
238. Hartroft, P. M., and Hartroft, W. S., *J. Exptl. Med.*, **102**, 205–12 (1955)
239. Blake, W. D., *Am. J. Physiol.*, **181**, 417–22 (1955)
240. Blake, W. D., *Am. J. Physiol.*, **181**, 423–27 (1955)
241. von Euler, U. S., *Ciba Foundation Colloquia Endocrinology-Human Adrenal Cortex*, **8**, 268–76 (1955)
242. Vogt. M., *Ciba Foundation Colloquia Endocrinology-Human Adrenal Cortex*, **8**, 241–53 (1955)
243. Doe, R. P., Flink, E. B., and Goodsell, M. G., *J. Clin. Endocrinol. and Metabolism*, **16**, 196–206 (1956)
244. Goldman, R., and Luchsinger, E. B., *J. Clin. Endocrinol. and Metabolism*, **16**, 28–34 (1956)
245. Teorell, T., *Exptl. Cell Research*, Suppl. 3, 339–45 (1955)
246. Foulks, J., *Federation Proc.*, **15**, 65–66 (1956)
247. Preedy, J. R. K., and Aitken, E. H., *J. Clin. Invest.*, **35**, 423–29 (1956)
248. Dignam, W. S., Voskian, J., and Assali, N. S., *J. Clin. Endocrinol. and Metabolism*, **16**, 1032–42 (1956)
249. Preedy, J. R. K., and Aitken, E. H., *J. Clin. Invest.*, **35**, 430–42 (1956)
250. Preedy, J. R. K., and Aitken, E. H., *J. Clin. Invest.*, **35**, 443–51 (1956)
251. Wise, B. L., *Proc. Soc. Exptl. Biol. Med.*, **91**, 557–60 (1956)
252. Stamler, J., Dreifus, L., Marcus, E., Wong, S., Hasbrouck, E. E., Sheridan, J. T., Maier, K., and Ellis, A., *J. Clin. Invest.*, **35**, 737 (1956)
253. Dempster, W. J., Joekes, A. M., and Oeconomos, N., *Ann. Roy. Coll. Surg.*, **16**, 324–36 (1955)
254. Murray, J. E., Lang, S., Miller, B. F., and Dammin, G. J., *Surg. Gynecol. Obstet.*, **103**, 15–22 (1956)
255. Bricker, N. S., Guild, W. R., Reardan, J. B., and Merrill, J. P., *J. Clin. Invest.*, **35**, 694 (1956)
256. Brull, L., Louis-Bar, D., and Marson, F. G. W., *Arch. intern. physiol.*, **64**, 269–77 (1956)
257. Goodman, H., Kay, J., Gaertner, R., and Baxter, J., *Federation Proc.*, **15**, 429–30 (1956)

258. Darmady, E. M., Dempster, W. J., and Stranack, F., *J. Pathol. Bacteriol.*, **70**, 225–31 (1955)
259. Kamrin, B. B., and Kamrin, R. P., *Anat. Record*, **122**, 223–39 (1955)
260. Kamrin, B. B., *Anat. Record*, **124**, 541–53 (1956)
261. Egdahl, R. H., and Hume, D. M., *Surg. Gynecol. Obstet.*, **102**, 450–62 (1956)
262. Surtshin, A., and White, H. L., *J. Clin. Invest.*, **35**, 267–71 (1956)
263. Watson, L. S., Gullixson, K. S., Rennie, D. W., Youmans, W. B., *Am. J. Physiol.*, **181**, 140–48 (1955)
264. Segar, W. E., Riley, P. A., Jr., and Barila, T. G., *Am. J. Physiol.*, **185**, 528–32 (1956)
265. Kanter, G. S., *J. Appl. Physiol.*, **7**, 533–36 (1955)
266. Blake, W. D., *Federation Proc.*, **15**, 20 (1956)
267. Földi, M., Kovách, A. G. B., Takács, L., and Koltay, E., *Acta Med. Acad. Sci. Hung.*, **8**, 19–36 (1955)
268. Földi, M., Kovách, A. G. B., and Takács, L., *Nature*, **176**, 120 (1955)
269. Cottier, P. T., Hoobler, S. W., and Weller, J. M., *J. Clin. Invest.*, **35**, 698 (1956)
270. Surtshin, A., and Latorre, G., *Am. J. Physiol.*, **182**, 524–30 (1955)

RECENT ADVANCES IN RUSSIAN NEUROPHYSIOLOGY

By W. T. Liberson

Veterans Administration Hospital, Northampton, Massachusetts

Introduction

This review covers the work of Russian neurophysiologists for the period starting January, 1950 and ending July, 1956. The reviewer realizes that his task could not be completed satisfactorily. His sources of information were limited to only a few periodicals which could be made available to him. Even such basic sources of information as the Sechenov journal could only be covered partially as most of the 1955 volume could not be located. Only a few publications from the countries under Russian influence could be located and reviewed. The material contained in monographs, publications of individual laboratories, textbooks, etc. almost completely escaped his inquiry. No reprints were available and no individual contact with Russian workers could complete the sources of his information. This review should, therefore, be considered as a first attempt to visualize the direction in which Russian neurophysiology has been developing during recent years with a full realization of the limitations of this undertaking.

Many findings of Russian neurophysiologists were independently disclosed by western workers. Many findings should be discussed in the light of the knowledge which may not have been available to the Russian neurophysiologists at the time of their publications. To do so, however, would be impossible within the frame of this review. The reviewer preferred to use the available space to give an account of the current research and theoretical conceptualizations of Russian workers rather than to attempt to integrate them into the edifice of contemporary neurophysiology as known to Western scientists. The past five year period of Russian neurophysiology is particularly interesting to review. Indeed, this was a transition from an era when the lack of modern equipment was conducive to theoretical speculations. Recent modernization of the laboratories found Russian workers ready to attack old and new problems with new tools and to turn more and more attention to the study of the concrete mechanisms of the observed facts rather than merely express them in terms of general concepts of inhibition and excitation as was done in the past.[1]

Excitability: Nerves and Muscles

Parabiosis.—One knows the long standing interest of Russian neurophysiologists in the study of Wedensky's "parabiosis," expressing the events

[1] Many papers in Russian journals are directed against western science and specifically American physiologists. As these attacks have mostly been inspired by political and idealogical reasons and as they seem to have disappeared recently, this reviewer omitted any specific reference to such criticisms.

observed during a growing conduction block in a peripheral nerve by a variety of agents, chemical or electrical (DC). The testing stimuli applied above the block elicit different effects according to the stage of "parabiosis." At the beginning, contractions of the same amplitude may be observed (stage of equalization) for stimuli of different intensity and frequency. This is explained by an increase of the block produced by more frequent or more intense stimuli reaching the area of the block. The next stage ("paradoxical") is characterized by a higher amplitude contraction elicited by the weaker or lower rate stimulation (the same explanations are given). The stage of a complete block is preceded by an ultra paradoxical phase when only weak or low frequency stimuli are effective. Ever since Wedensky's time, these phenomena were related to electrotonic "syndromes" at the level of the block with a "stationary state of excitation." First, an "anelectrotonic syndrome" (stage of equalization) and then a "stationary state of inhibition" corresponding to a "catelectrotonic syndrome" characterized by a paradoxical stage. The anelectrotonic syndrome is associated with a maximal lability (conduction of stimuli delivered at the highest rate), decrease of the refractory period, decrease of the chronaxy, and tendency to autorhythmicity. Just the opposite characterizes the catelectrotonic syndrome. Latmanisova (1) studied these changes in relation to the modification of the accommodation constant (lambda). Some of this work was done on single fibers. The first phase of "parabiosis" produced by an isotonic solution of potassium chloride is associated with a decrease of lambda up to a "breakdown of accommodation." Oushakov *et al.* (2) found that within a period of 30 msec. following an establishment of a DC polarization there is a decrease of excitability with "cathodization" and an increase of excitability with "anodization."

Chronaxy and "lability."—A controversial discussion was originated by Nassonov & Rosenthal's criticism [(3), cf. (4), also (5)] of a tendency of Russian neurophysiologists to use chronaxy as an exclusive index of neuromuscular excitability. The main point of these investigations is that the chronaxy, being expressed by the quotient a/b according to the Weiss-Hoorweg equation, should be influenced considerably by independent changes of the rheobase (b) without concommittent change in the temporal course of excitation. Oufland (5), representing Wedensky-Ouchtomsky's school, considers chronaxy as an index of the "mobility" or "lability" of the excitatory processes in the nervous tissue only insofar as the initial process of excitation is concerned. It is the maximum rate of stimuli which may be handled and conducted by the tissue which constitutes the basic index of "lability" as accepted by this school. Hence, a great number of papers have appeared in Russia related to this index and to its modification under the influences of the centers (by analogy with "chronaxy" of subordination). When the sciatic nerve of the frog is stimulated at a maximum rate (up to 600 cycles per sec. for 1 to 3 sec.) lower rhythms are picked up from the muscle, the "coefficient of transformation" being of about 2 (the rhythm

being halved) in a thalamic frog, about 3 in a bulbar frog, and 3.5 to 4 after the section of the nerve [Levitina (6)]. The same author studied in 1953 (7) the "autonomous" rhythm of the spinal cord as expressed by a maximum rhythm of muscle potentials picked up in the semitendinosus and gastrocnemius muscles following electrical stimulation of the lumbosacral cord or chemical stimulation of skin receptors. The initial rhythm of 60 to 130 cycles per sec. was decreased by 20 to 60 per cent after subcollicular decerebration. In these and in previous experiments, single units were not studied. Miminoshvilli (8, 9) found that a nerve in a process of regeneration follows at first rhythm of 50 cycles per sec. and finally acquired 300 cycles per sec. rhythm (instead of 500 cycles per sec. normally). Frog sciatic nerve was either sutured after a section or its conductibility was interrupted by pinching. Fifteen to 45 days after the operation nerve potentials were recorded above and below the level of the injury. The activity in the nerve was induced either by injection of strychnine (to test centrifugal impulses) or by proprioceptive and skin stimulation (to test centripetal impulses). In both cases, the frequency and amplitude of potentials were decreased (their duration was increased) below the level of the injury, while there were normal rates observed above the injury. There was, therefore, a "transformation" of the rhythm from fast to slow and from slow to fast according to the direction of the conduction. Interaxonic conduction in the regenerated nerves at the injury level was suggested. Danielson (10) found that after denervation there are changes in the index of "lability" in the symmetrical muscles of the opposite side. These muscles show a contracture during stimulation and their weight may decrease by 40 per cent [Ermakov & Medvedeva (11)]. Khrolinsky (12) found that the demarcation current of the frog gastrocnemius decreased during the first six hours following denervation. It decreases after sectioning of the spinal cord. It decreases slightly but remains at a high level after a section above the thalamus. Under such conditions, a cathodal polarization of the thalamus slightly increases (10 per cent) the demarcation current of the muscle, while anodal polarization decreases it (15 to 20 per cent). Chemical stimulation of the thalamus increases this potential only in the presence of the sympathetic chain, provided that the spinal cord remains intact. Motzny (13) found that a crystal of sodium chloride put on the thalamus of the frog slows down accommodation in the peripheral nerves, while the section of the spinal cord has no effect. Popov (14, 15) found that anodal polarization of the lumbar spinal cord increases and cathodal polarization decreases the amplitude of muscle contractions elicited by direct stimulation.

Tonic versus tetanic contraction.—In Russia, as elsewhere, physiologists are divided among themselves as to the specificity of tonic innervation. Most of them, however, agree that the low "lability" of the corresponding structures is the decisive factor. Sharitova & Zhukov (16) repeated the classical experiments of Biscoe on cats and rabbits. Stimulation of the sectioned femoral nerve produces either tonic contractions, or tetanus of the

quadriceps, according to the frequency of stimulation. Other factors are also important (depth of anesthesia, state of excitability near nerve section, etc.). Tetanic and tonic activities may be differentially affected at different stages of excitability changes induced by a polarization of the nerve. Distinct structures are related to either tonic or tetanic components of the muscle contractions. Thus, the lateral head of the muscle shows minimal tonic components of the contractions under different conditions of alteration of the nerve. Its potentials have a characteristic diphasic form. In the other parts of the muscle, monophasic potentials predominate and when diphasic potentials are observed, the second phase shows an unusually prolonged duration. In addition, these portions of the muscle show a low amplitude asynchronous activity. However, under certain conditions of the alteration of the "lability" of the preparation, an asynchronous activity may appear in the vastus lateralis and diphasic potentials in the rest of the muscle. Sorkov (17) found that, while any isolated muscle fiber of the semitendinosus of the frog is capable of a slow tonic contraction, not all of them are capable of developing a tetanus.

Zirmoonskaia (18) showed that single stimuli elicit in the nerves of the anodonta negative potentials with an ascending phase lasting for .2 to .7 second and a descending phase lasting for .8 to 2 seconds. These negative potentials are followed by a prolonged positive wave. Repeated stimulation (8 stimuli per minute) produces a decrease of the amplitude of successive negative potentials which may be explained by a summation of positive after effects. For frequencies above 60 stimuli per minute, there is a superimposition of negative potentials as well, resulting for the highest frequencies of stimulation in a constant negative polarization of the nerve. Electromyograms show a succession of "slow" spikes as long as individual negative potentials are recorded in the nerve. As soon as a continuous negative polarization appears in the nerve (high frequency of stimulation), no potentials could be recorded in the muscle despite the presence of a tonic contraction. The author believes that tonic contractions are not associated with spike potentials. No microelectro-oscillographic exploration was performed however.

Kostuk (19) studied the effects of paired stimuli by microelectrography of muscle fibers. When the interval between two consecutive stimuli was of 7.5 msec., potentials of about equal amplitude could be recorded at the aneural end of the muscle fiber, while near the endplate, the second potential was of lower amplitude. When the interval was below 6 msec., the second potential was still lower and no conduction was evident at the other end. During a relative refractory period, the spike velocity was slowed significantly. Different muscle fibers were classified according to duration of their relative refractory period which was found of 10 to 15 msec. for the fibers of highest velocity, and of 30 msec. for the slowest fibers. The author claims that there are muscle fibers which do not respond to stimuli with any potential.

Receptors

Chronaxy.—Rheobase and chronaxy determinations are claimed to be useful in exploration of the optic and vestibular mechanisms. Rudnik (20) found slight changes in the chronaxy determined by a lateral stimulation of one eye following a medial polarization of the other eye. This effect is presumably due to a retrograde "subordination" mediated through the crossed optic path on one side and the ipsilateral optic system on the other. Rheobase did not change. The same author finds rheobase changes in patients with homonymous hemianopsia in localized occipital lesions. In these cases, the rheobase was determined by placing the stimulating electrode on the lateral corner of each eye. Cholinergic substances increase and adrenergic agents decrease optic chronaxies. Vestibular chronaxies were found to be low in patients with a marked autonomic system disbalance (5.6 to 12.8 msec. instead of normal 19 to 24 msec.).

Infraliminal stimuli.—Gershouni (21) gave a detailed account of his stimulating work on perception of "infraliminal" stimuli, using conditioned skin galvanic reflexes and alpha block reactions. (The unconditioned stimulus was an electrical stimulation of the hand.) At first it was ascertained that sound (1000 cycles per sec.) of 6 decibels below the threshold determined by verbal accounts was never subjectively audible. Despite this, such infraliminal stimuli could elicit definite conditioned reflexes. However, the reaction times of the skin galvanic reflexes to the infraliminal stimuli were significantly longer than in the case of supraliminal ones (1½ to 4 sec. instead of 1 to 2½ sec.). Alpha block was more prolonged for supraliminal stimuli. According to the author "reaction of orientation," increasing the level of cortical excitability, is missing when infraliminal stimuli are applied.

Electrical potentials.—An excellent electrophysiological analysis of the function of venous thermoreceptors was made by Minute-Sorokhtina (22). Intercostal nerve twigs were found transmitting potentials of venous thermoreceptors of superficial thoracic veins. The latter were either left *in situ* or completely dissected. Temperature could be changed either in the surrounding tissues or intravenously by an appropriate perfusion. In the latter case, the temperature was between 14 and 40°C. Potentials of about 40 mv. were recorded in the nerves, their velocity being 9 to 15 meters per sec., corresponding to myelinated fibers of 5 to 10 microns. The electrical activity was a function of the actual temperature and not of its gradient in space or time. The lower the temperature, the more "active" the oscillogram was, as there was evidence of recruitment of additional receptors. There was no evidence of distinct "warm" and "cold" points. No adaptation was found during trials lasting several minutes. A reversible block could be produced at 15°C. Novocain would also produce a block after a short stage of hyperexcitability.

Roitbak & Cherinatvili (23) challenged the interpretation of Adrian's findings relative to the 50 cycles per sec. activity recorded in the olfactory bulb following olfactory stimulation. In contradistinction to Adrian's con-

clusions, they do not believe that these potentials are of nerve origin as they persist after cocainization of the olfactory bulb or its removal. They may be recorded from the intranasal bony and cartilaginous structures during each inspiration. They are particularly prominent when air is projected upon posterior structures of the nasal cavity and believed to be related to the mechanical vibrations. If the origin of some of the bursts of fast activity recorded in the olfactory system appears controversial to these workers, their transmission within the central nervous system appears to be related to specific structures. Thus, Novikova & Khvoles (24) found the bursts of 40 to 70 cycles per sec. oscillations (1 mv.) on top of slow waves along olfactohypothalamic tracts down to the anterior hypothalamus. No such bursts were recorded at 1 mm. distance from the activated structures and none were found in the posterior hypothalamus, thalamus, or temporal and occipital cortices. These bursts, barely discernible at rest, were clearly related to mechanical stimulation of intranasal passages and were considerably increased in amplitude by concommitant emotional or painful stimuli. They are then associated with a decrease of the spontaneous activity in the diencephalic structures. They occur at the height of inspiration and can be observed in tracheotomized rabbits when air is blown through the nasal passages. They are suppressed in the neuronal structures by intranasal local anesthesia or section of the filae.

Spinal Cord

Electrography.—The reviewer found only few papers dealing with electrography of the spinal neurons, none as yet with microelectrography. Vorontzov (25) found that in frogs excitation of the ninth lumbar root (dorsal) evokes initial catelectrotonic potentials on the eighth dorsal root on the same side but anelectrotonic potentials on the seventh dorsal root on both sides. In the same experiments, ventral roots show either negative or positive potentials according to the dorsal root involved, usually positive electrotonic potentials predominating in the distant roots. Kostuk (26) denies a close relationship between the amplitude of electrotonic potentials and spike discharges, although such a relationship is revealed by his tracings in the case of plurisynaptic reflexes. He (27) believes that the initial inhibition of reflexes induced by an antidromic impulse (for about 3.5 msec.) expresses the refractory stage of the axon itself and not that of the motor neuron. In favor of this interpretation, he invokes the presence in the neighboring neurons of all other phases, except the initial depression.

Encephalospinal relationships.—Cherkess (28) found that cortical inhibition of ipsilateral flexor reflexes in cats is not suppressed by an ipsilateral hemitransection of the spinal cord. He concludes that the effect is attributable to inhibition induced by contralateral structures of the spinal cord influenced by crossed descending cortical neurons. Stimulation of the striatum and tectum elicits inhibition of ipsilateral spinal reflexes through pathways descending on both sides of the cord. Mnoukhina (29) describes a suppres-

sion of reciprocal inhibition of flexor reflexes in decerebrated cats by stimulation of the cerebellum (the locus of stimulation is not indicated).

A series of papers stem from the original publication of Tonkikh appearing years before the period covered in this paper. Tonkikh repeated the classical experiment of Sechenov: a crystal of sodium chloride put on the cut surface of the thalamus in a thalamic frog produces inhibition of the spinal reflexes. She found that this effect is suppressed by section of all the rami communicantes. Strakhov & Ouspevitch (30) confirmed analogous findings in regard to thalamic inhibition of the heart in frogs. Complete sympathectomy prevents this cardiac arrest; any remaining ramus makes arrest possible. A direct stimulation of the medulla in such an animal elicits bradycardia despite bilateral sympathectomy. On the other hand, injection of epinephrine may restore Sechenov's inhibition. The author explains these findings by a postulated activating effect of the sympathetic system upon the medulla. Goumenuk (31), working on frogs, found that the "rebound" phenomenon, following the end of reciprocal inhibition of spinal reflexes, disappears during thalamic activation. This is, however, not observed after sympathectomy or an injection of ergotoxin. Senkevich (32) studied the effects of the adrenals on Sechenov's inhibition. Starting with the fourth day after bilateral adrenalectomy Sechenov's inhibition cannot be elicited in frogs. Daily injections of epinephrine prevent this effect of adrenalectomy. This phenomenon seems therefore to be of an hormonal nature.

Volkova (33, 34) found that perfusion of the veins of the spinal cord during inhibition of spinal reflexes produced by stimulation of the peroneal nerve (with recording of the contraction of the semitendinosus) reveals the presence of "inhibiting substances," as the fluid injected into another animal inhibits spinal reflexes. As this action is prevented by cholinesterase, the inhibiting substance is believed to be acetylcholine. In pancreatectomized frogs, inhibition of flexor reflexes could not be obtained by the stimulation of the brachial nerve after the seventh postoperative day. Injections of acetylcholine beginning on the fourth postoperative day prevented the effects of pancreatectomy.

Cerebral Potentials

There is a rapidly increasing number of studies during recent years concerning electrical activity of the central structures. Several papers were devoted to the techniques of "chronic" implantation of electrodes for studies on nonanesthetized animals, particularly during conditioning. Recording techniques are adequate; however, cerebral microelectrography has not been, as yet, reported in the material available to the reviewer.

Cortical electrography: basic studies.—Much challenging work comes from the Beritoff Laboratory. Roitbak's monograph (35) gives an account of work done by Western electrophysiologists from Adrian, and Rosenblueth & Cannon to the latest publications of Bishop & Clair, in the light of personal contributions and with an attempt to integrate this work into the major

themes of Russian physiology: Wedensky's parabiosis, Ouchtomsky's "dominanta" and Pavlov's conditioning. Beritoff (36) attempts to express conditioning in terms of cytoarchitechtonic and electrophysiological data. The available space permits us to give only limited glimpses of the work of this laboratory. Surface negative potentials induced by electrical stimulation of the cortex may be summated by a repetitive stimulation (35). Steady or slowly pulsating potentials result from such summation. Negative polarization may be followed by a positive one and mirror images of these changes are found in the deep regions of the cortex. These changes are ascribed to the polarization of apical dendrites which, according to Roitbak, do not conduct but effect electrotonically the bodies of the pyrimidal cells. According to Beritoff & Roitbak (36, 37), this is a basic mechanism of a generalized inhibition of the deep layers of the cortex, deep anelectrotonus resulting from the surface catelectrotonus. According to Beritoff, basal dendrites of pyrimidal cells have inhibitory functions also but more differential ones than in the case of the apical dendrites. Roitbak (35) recorded a considerable spread of the surface negative potentials following focal cortical excitation in nonanesthetized animals. Thus, Wedensky's hypothesis of the electrotonic nature of inhibition resulting from high frequency of stimulation seems to find its expression in the work of this laboratory. On the other hand, according to Roitbak (37), the after-discharge elicited in a limited area of the cortex represents a focus of increased excitability. Thus, if after cessation of high frequency stimulation single stimuli are applied, their effects are considerably potentiated during one minute or so. Cholokashvili & Roitbak (38) claim that there are changes in the appearance of the cells (less prominent contours of the nucleus) in the area of the posttetanic potentiation. Strychnine spikes are often synchronous with respiratory movements, cortical neurons thus becoming responsive to subliminal afferent stimuli originated in the respiratory centers. This is believed to be an expression of Ouchtomsky's "dominanta." Strychnine in high concentration decreases negative potentials of the cortex. According to Beritoff (36), conditioned links can be formed within the third and fourth layers through internuncial and association neurons (small and medium pyramids). When the star cells are implicated, conscious perception takes place. "Two way" temporary connections are made with the participation of these cells. The formation of such connections is associated with functional and morphological changes in the cells and synapses which are believed to be correlated with a thickening of the nerve fibers involved in these connections. Mechanisms explaining inhibition surrounding the foci of excitation are postulated by Beritoff and Roitbak on the basis of inhibitory functions of dendrites.

Subcortex.—Alexanian (39) reveals that there is a dissociation between the effects of sensory stimuli (visual and auditory) upon the background activity respectively in the cortex and certain subcortical areas. While the former shows a desynchronization, the latter usually responds by an hypersynchronization of 5 to 7 cycles per sec. activity. The author did not explore

the rhinencephalon where such response has been generally described, but found it in the thalamus, caudate nucleus and colliculi. Grastyán *et al.* (40) devoted a major study to the cortical electrical manifestations of diencephalic inhibition. These authors differentiate different types of cortical effects according to the frequency of stimulation applied to various diencephalic areas. The cortical effects are tested by changes in muscle contraction induced by the stimulation of the motor area and by the modification of the electrical activity of the cortex. Stimulation of anterior thalamic nuclei, particularly the anterior pole of the anteroventral, centrolateral and dorsomedial nuclei always produce inhibition of the cortically induced movements regardless of the frequency of stimulation. Stimulation of the remaining areas of the dorsomedial nucleus, nucleus ventralis anterior, as well as of intralaminar and reticular thalamic nuclei, produces results which differ according to the frequency of stimulation and the location of the stimulated points. There are two types of reaction. When frequency of stimulation applied to certain loci is between 25 to 50 cycles per sec., inhibition is produced. When the frequency is above 100 cycles per sec., facilitation is observed. The frequency effect was different when other points of these nuclei were stimulated. In these cases, intermediate frequency of 50 to 200 cycles per sec. produce facilitation while slower and higher frequencies of stimulation induce inhibition. Whenever inhibition was elicited, a slow electrical activity in the cortex was induced. Such activity was observed even when stimulation of high frequency was applied to the anterior nuclei.

Anesthesia and sleep.—The presence of slow activity is believed to serve as an index of reciprocal or synergetic inhibition in the cortical and subcortical structures. Robiner (41) studied such relationships during different stages of ether anesthesia in the cortex (anterior ectosylvian gyrus) and the thalamus of cats. During the initial excitatory state, fast activity disappears in the corticogram. The cortex may show at that stage 1 to 2 cycles per sec. slow activity with superimposed 4 cycles per sec. waves. On the contrary, the thalamus (ventral and lateral nuclei) shows a disappearance of the delta components which may be recorded there during the waking state, and an activation of 8 and 15 to 18 cycles per sec. activity. This period is said to be very short (of the order of two minutes) and may be easily overlooked. The next stage is characterized by an increase of delta activity in both thalamus and cortex. This is the stage when reflex action is absent. After suppression of narcosis, fast activity returns first in the thalamic nuclei, then in the cortex; as reflex action is progressively restored, thalamic fast activity decreases. Such are the changes in electrical activity, at least when anesthesia is of short duration (30 to 60 min.). In the case of more prolonged anesthesia, 10 cycles per sec. "alpha" rhythm (which appears, however, to the reviewer as "spindle-like") appears mostly in the thalamus after the removal of the mask. In the case of a very prolonged narcosis (over two hours) this spindle-like activity invades different regions of the brain and lasts for a considerable length of time. According to the author, the cortex

first shows signs of inhibition at the beginning of narcosis while the presence of a transitory fast rhythm in the thalamus expresses its liberation from the inhibitory action of the cortex. Only later inhibition spreads over the thalamus.

Alternation of waves of inhibition and excitation is detected by Gouliaev (42) in the human EEG's during sleep. As is well known, sensory stimuli applied during sleep may elicit a burst of fast activity which expresses, according to the author, a wave of excitation. There is a refractory phase of about 7 to 10 seconds following such a burst, during which a second stimulus fails to induce another burst. The duration of a relative refractory stage is of about 20 seconds. This corresponds to a wave of inhibition. If the subject received a preliminary instruction to squeeze a rubber bulb in response to a sensory stimulus, the reaction time is shorter during the burst than at its onset. If stimuli are of different nature, for instance, auditory and visual, the same time relationships may be found as to the duration of the refractory stage. This would signify that the wave of inhibition involves the whole cortex. At times, however, a tactile stimulus may prove to be effective while the auditory one is not, which leads the author to formulate additional hypotheses.

There are several papers comparing natural and hypnotic sleep which causes some embarrassment to the writer (43, 44). Indeed hypnosis has been considered by the Pavlovian school as an expression of inhibition and yet the pattern of electrical activity during hypnosis is not very different from a waking tracing according to generally accepted findings.

Epileptic discharges.—Rozhansky (45) confirmed in 1953 that regions located close to the fornix are most epileptogenic. Kreindler (46) summarized a great number of studies which he carried out with different associates. The following are the most intriguing findings: (*a*) In a dog with chronically implanted electrodes, Jacksonian seizures produced by cortical stimulation were associated with auditory stimuli; the latter could then elicit a conditional seizure. The number of associations required is very high. It would be of interest to see whether a pathological alteration of the cortex is necessary in order to elicit such a reflex. (*b*) Electrically induced seizures are at times followed by spontaneous clonic fits. This was found only when thalamic lesions involving the center median were found. (*c*) During and after seizures there are rhythmic contractions of the spleen. The latter disappear after decortication. (*d*) Free acetylcholine decreases in the venous blood of the brain after seizures, while the bound acetylcholine markedly increases. (*e*) After a seizure conditioned reflexes involving the autonomic nervous system are restored more quickly than those involving the somatic nervous system.

Metrazol sensitivity expressed by convulsive threshold in mg. per kg. of the drug decreases from fish to men in a ratio of 1 to 25; amphibians, reptiles, and mammals showing progressively decreasing intermediate thresholds. The electric convulsive threshold also decreases proportionately from frogs to mice, although differences in current distribution make such comparisons

difficult. Electrically induced seizures are less stereotyped in lower animals than in mammals. Thus, in frogs, there is an irregular succession of clonic and tonic states. Tzobkallo (47) found that excitation of the hypothalamus between the tuber cinereum and the mammillary bodies produces an arrest of convulsions induced by metrazol injections. On the other hand, implanted needles producing injuries in the posterior hypothalamus increase convulsive threshold to metrazol.

Cortical potentials and conditioning.—In the field of electrographic correlates of conditioning, Russian neurophysiologists have done pioneering work. Artemiev (48, 49, 50) called attention to the variability of evoked cerebral potentials in nonanesthetized cats. He recorded evoked potentials in nonanesthetized animals from what he believed to be the primary auditory cortex. The latency times of the reported evoked potentials are, however, 15 to 50 msec. During a series of 5 cycles per sec. auditory stimuli only the first stimulus may be effective. Even when the stimuli were delivered at a rate of 2 cycles per sec. the amplitudes of evoked potentials were quite variable. At times, no response was obtained even for the rates of stimulation of two per minute. However, if the character of the auditory stimulus is suddenly modified, evoked potentials reappear. The same effect is seen if an additional extraneous stimulus is applied. Evoked potentials (at first their negative components) disappear during the normal sleep. According to Roitbak (51) evoked responses during the waking states are characterized by the appearance of generalized bioelectrical reactions, the long duration of the after effects, the complex character of the primary responses, and the extreme variability of the reactions. The additional components of the reactions (an additional positive potential, an alpha-like wave, a prolonged change of spontaneous activity) are believed to be caused by a discharge of a considerable number of neurons of the third and fourth layers. During natural sleep, the primary response is limited to a positive potential of increased amplitude which would be explained by a local excitation of the neurons of the third and fourth layers; a volley of afferent impulses reaching the cortex does not evoke (as it does in a waking state) a discharge of these cells either in the ascending axons or in the associative fibers. During further investigations, also performed on cats, Artemiev & Besladnova (50) correlated their findings with conditioning. An auditory stimulus (1,000 cycles per sec.; duration, 1.3 sec., 60 db. above the human threshold) was associated with a painful electrical stimulus, elicited .8 sec. after the beginning of the sound. Evoked potentials were recorded from the acoustic area; electromyograms were also recorded. At first evoked responses disappear. The authors ascribe this finding to the inhibiting effect of the painful stimulation. There is no constant relationship between the presence of the "reaction of orientation" and the presence of evoked potentials. A conditioned reflex was established after 5 to 80 associations. Shortly before the conditioning was established evoked potentials reappeared. Never was conditioned reflex formed without a preliminary reappearance of evoked potentials. On the

other hand, their reappearance was not necessarily followed by an establishment of conditioning. When conditioning was firmly stabilized, evoked potentials could disappear again. The authors explain this by "re-routing of excitation" toward the motor area. They believe that the presence of evoked potentials during the stage of preconditioning is related to a certain level of excitability of corresponding neuronal structures; their disappearance may be explained by either external or internal inhibition. In order to at least partly test this hypothesis, Artemiev conducted experiments during which mustard plaster was applied to the skin of animals which were selected for the stability of their evoked potentials. Under such conditions these potentials disappear. Application of strychnine to the motor cortex also suppressed evoked potentials in the acoustic area. This finding is explained by a "negative induction." Lurie & Trofimov (52) also described evoked potentials in the acoustic area of nonanesthetized animals with a latency of 30 to 100 msec. When stimuli (.2 to .3 sec. duration) were repeated at a frequency up to 5 cycles per sec., the original sharp potentials were replaced by regular oscillations persisting one-half to 1 second after the end of the stimulation. During formation of motor conditioned reflexes an increase of the fast background activity in the motor cortex was observed. Sakhoulina (53, 54) studied conditioned defense motor movements in dogs. Predominance of a diffuse fast activity (30 to 40 cycles per sec.) was recorded by chronically implanted electrodes during the period of "adjustment" of the animal to the experimental condition. When EEG was stabilized, and fast activity disappeared after a certain preliminary period of time, the training of the animal for conditioning was started. This was associated with a reappearance of a generalized fast rhythm. In the more advanced periods of training, reappearance of the fast rhythm was seen only during application of stimuli. When conditioning was firmly established, the fast rhythm was found only in the opposite hemisphere and finally only over a limited area of the motor cortex. In these experiments, the implanted electrodes were insulated down to the tips but the pericranial muscles were not denervated. Peimer & Fadeeva (55) investigated conditioning of alpha blocking reaction in man. The subject was ordered to either squeeze or not to squeeze a rubber bulb, these orders being preceded respectively by a positive and a "differential" conditional stimulus. The conditioned alpha blocking reaction was followed in many cases by bursts of slow potentials (3 to 5 cycles per sec.; 30 to 50 min.). Differential stimulus at first produced a marked alpha blocking reaction, then was followed by its extinction. Slow activity is usually explained by Russian neurophysiologists as an expression of "inhibition." However, there was no slow activity during extinction elicited by the differential stimulus. The authors attempt to explain this unexpected finding by an assumption of an undetected localized inhibitory process. Interesting results were also observed in the case of a "consecutive inhibition" (when the effect of a positive conditional stimulus is inhibited because it follows closely a negative differential stimulus). There is then an increase of the reaction time, de-

crease of the motor reaction, and a weakening of the alpha blocking reaction. Finally an interesting observation was made on one of the members of the staff familiar with the purpose of this study. This subject consciously tried not to squeeze the bulb despite positive conditioned stimuli and reinforcing verbal stimuli. During these attempts, the EEG blocking reaction was considerably increased and a great deal of secondary slow activity appeared in the tracing.

In an attempt to test the hypothesis of Ouchtomsky in regard to the role played by "dominant" processes in the genesis of conditioned reflexes, Rusinov (56) carried out an interesting study. A DC polarization of a segment of the motor cortex in a cat results in jerks of the corresponding extremity each time a previously nonspecific stimulus is produced (for instance, an auditory one). Analogy with the mechanism of reflex epilepsy is obvious. Naoumova (57) gives further experimental analysis of this phenomenon. The author shows that this effect of auditory stimuli can be seen only under certain conditions. She shows that a "dominant focus" can be established only when polarization causes an increase of the background fast activity and when the latter can be further intensified (within certain limits) by the auditory stimulus. When cortical polarization elicits slow oscillations, the Rusinov phenomenon either is not seen or other extremities are activated instead of those corresponding to the area submitted to the action of DC. During such polarization, oscillations synchronous with heart beat or respirations were recorded. This was interpreted as a sensitization of the cortex toward incoming stimuli of cardiac or respiratory origin. Novikova & Farber (58) show that stimulation of one eye in rabbits drives the electrical activity of the contralateral occipital cortex with a residual intensification of the background rhythm. At that time, auditory stimuli may reinforce this activity which thus expresses the presence of a "dominant focus." If such an occipital focus of dominance is created by anodal polarization, the effects of both visual and auditory stimuli are reinforced. If anodal polarization results in paroxysmal activity, the latter spreads not only over cortical areas, but over the contralateral retina as well. In such a case, the retinal activity is synchronous with the cortical after discharge.

According to Roitbak (35), a high frequency cortical stimulation (50 cycles per second) applied simultaneously with a low frequency stimulation (5 to 10 cycles per second) at a distant cortical region, potentiates or changes the polarity of the effects of the latter, or produces both effects, even after the end of the tetanizing activation. If, however, there is no overlap in time of both kinds of stimulation, potentiation may not be observed. A model for electrophysiological processes related to conditioning is seen in this experiment.

Conditioning

Strength of stimuli.—It is common knowledge that strength of conditioning reflexes usually depends upon "reinforcement." For feeding reflexes

(salivation), Lomonos (59, 60) found that the first 30 sec. of reinforcement are critical for this relationship. If the quantity of "unconditioned" saliva during this period is excessive, the processes of conditional inhibition are affected; differentiation becomes difficult. The amount of food given during the reinforcement becomes a sort of conditional stimulus for a certain level of excitability during a prolonged experiment: the amount of food given after the first conditioned stimulus predetermines how the animal will respond to all the remaining stimuli constituting a "stereotype." A "stereotype" is made of several conditional stimuli, positive and negative, succeeding each other in a certain order.

Not only does the degree of reinforcement influence the level of conditioning but also the latter influences the amount of "unconditioned" saliva [Fedorov (61)]. The basic finding is that the amount of saliva secreted during reinforcement is below that of "unconditional saliva" secreted in response to the same food, before the establishment of conditioning. This is explained by a "negative induction" of the stimulated cortex upon the "subcortex." If the conditioning is made stronger, this negative induction becomes more intense, and therefore unconditioned saliva during the periods of reinforcement is still more reduced. On the contrary, if the conditioned reflexes are made weaker (by delaying reinforcement), the unconditioned salivation becomes more abundant because of the decreasing "negative induction." For Russian "conditionalists" a stronger conditioning signifies a "concentration" of excitation in the cortex and a strong negative induction of subcortical processes. A weaker conditioning means irradiation of excitation toward subcortex and, therefore, weakening of the negative induction. Such conceptualizations are quite flexible. For instance, the same author (62) states that the relationship between the strength of external stimuli and the intensity of the conditioning may be modified by supraliminal inhibition and the ability of the cortex to establish its own scale of the relative intensity of stimuli.

Irradiation.—The concepts of irradiation, concentration, and inhibition may be illustrated by the studies of Lapina (63, 64). Local unilateral chemical stimulation of the tongue by hydrochloric acid produces a much stronger activation of the ipsilateral than of the contralateral salivary glands, the ratio being 5 to 1. This was ascertained after appropriate surgical procedures on chronic animals. After a repeated unilateral stimulation, the gland of the opposite side ceases completely to respond unless the intervals between the stimuli are too long (once a day; in such a case, both glands remain active). According to the author, there is at first generalization of excitation, then concentration. She then conditioned the animal to auditory stimuli preceding the application of the acid simultaneously to symmetrical points of the tongue. If the stimuli are of equal strength on both sides, bilateral salivation results. If the stimuli are stronger on one side, only ipsilateral glands are conditioned, those on the opposite side being inhibited.

Switching.—The phenomenon of "switching" is one of the main tools of Russian conditionalists used to test the "mobility" of the underlying neuro-

physiological processes. Krassousky (65) studied this problem. For instance, the reversed order of three different components forming a positive conditional stimulus is made a "negative" stimulus (by nonreinforcing it). Then these two chains of stimuli are changed as to their significance for the animal. For instance, they may now signify the appearance of danger instead of food. Certain dogs may handle these problems very easily, while others break down. Such experiments contribute to the typological study of the animals. The switching is easier if different "analyzers" are involved, for instance, when an optic signal acquires the same significance as an auditory one, and vice versa). Switching within the same analyzers is particularly difficult if the difference between the stimuli is one of intensity. Alexeeva (66) found that switching from the "optic analyzer" to the auditory system is easier than the other way around. Switching may consist only in changing the experimental room or the laboratory personnel, and, therefore, may involve a general "environment" [see Beritoff (36)].

Effect of pain, emotion and conflict.—Painful stimuli [Fedotov (67)] affect conditioning differently according to the personality of the dogs. The work of Norkina (68) is related to the effects of very intense emotional stimuli such as gun shots, projections of stones, fire, etc., upon conditioning in dogs. The animals were trained to react to a signal by depressing a lever which operates the introduction of food in the chamber. The conditioned reflexes were depressed and the animal would not come near the lever. It would eat, however, if the food was given to it directly. This observation suggests to the author that emotional stimuli elicited in this setting affect defensive reactions of the animal expressed by a reactive hypomobility. The stimuli do not act upon the "centers" of feeding mechanisms. If this were the case, the animal would continue to press the lever but would refuse to take food, as happens when the animal is overfed.

A detailed analysis was made by Kurtzin (69) of gastric and pancreatic secretion following a conflict between defense and feeding reactions. During such experiments, the dog is given food which closes a contact of a battery delivering an electric shock to the animal. After only one association of this kind, gastric and pancreatic secretions may be modified for weeks. The current alone has no effect. A still more elegant technique is described under the name of cat-mouse experiments. In this experiment, a battery is connected by long wires to the tail of a mouse and to the tail of a cat. Both are then turned loose. When the cat catches the mouse she is shocked by electrical current which produces a nervous "breakdown."

Biological significance of stimuli.—Findings of this kind, which have been known to western experimental psychologists for some time, make Russian conditionalists pay more attention to the biological significance of stimuli used in conditioning techniques. Some workers doubt whether the current techniques are designed properly to take into account the significance of certain situations to the animal. For instance, Gambarian (70) analyzed the significance of the classical conditioned defense reflex. In this technique the

"reinforcing" stimulus is applied to a rising leg of an animal; it makes this motion biologically meaningless. The author explains many neurotic reactions in the experimental animal by the lack of biological significance of the induced movements. One may, however, establish a more meaningful reflex by following Petropavlovsky's technique. With this method the current is closed five seconds after the beginning of the conditioned stimulus; by raising its leg, the animal breaks the current. A stable conditioned reflex is then obtained. However, with this technique, the animal learns to avoid the stimulus for months. Under such conditions the reflex disappears but is re-established after only one association. By changing the timing of the reinforcement, one may produce two opposite reflexes, one consisting of leg rising and the other of pressing the paw against the table. Troublesome problems then arise for the classical theorists of conditioning; what is the mechanism of the conditioned movements which are exactly of an opposite direction to the unconditioned motor acts (extension during pressing against the table and not the flexion induced by stimulating current)?

Fedorov (71) discusses another interesting experimental finding. It is easy to induce conditioned behavior in a dog by feeding him each time he scratches his food box. However, if after his scratching one food box, one feeds him from another one, conditioning is more difficult to establish and the induced scratching is much weaker. Obviously the difference is related to a more meaningful behavior, when the dog scratches the box from which he gets his food. In general it is very difficult to establish a conditioned reflex involving voluntary movements of a dog. For instance, a conditioned reflex was established to a leg movement, this movement being reinforced by feeding. Then an attempt was made to produce this movement in response to an auditory stimulus (metronome); only then the dog was fed. After a considerable number of associations, this was achieved only if the movement was immediately followed by feeding. If, however, feeding was delayed by half a minute, no movement could afterwards be elicited by the sound of the metronome.

The complexity of problems involved in the animal perception of environment is illustrated by the following experiment carried out by Daniarov (72). Natural (obviously also conditioned) salivation markedly decreases with the increase of the distance between the animal and food (piece of meat). Olfactory perception can be ruled out by putting an object simulating a piece of meat. One might think that it is the extent of the area of the retina stimulated by the food which controls the amount of salivation, this area being reduced by increasing the distance between the object and the animal. It is not so, as an equivalent increase of the size of the object placed at a greater distance further decreases salivation. Also dimming of light when food is located near the animal does not decrease the amount of saliva.

Inhibition.—Problems of inhibition have been historically in the center of interest of Russian neurophysiologists. Sechenov introduced the notion of central inhibition as a result of thalamic stimulation in frogs. Wedensky

formulated a celebrated theory of inhibition based on parabiosis. According to his theory, repeated action potentials reaching a tissue of lower "functional mobility" ("lability") contribute to the development of a cathodal depression resulting in inhibition. Pavlov classified different inhibitory processes as unconditional and conditional and among the latter recognized a variety of forms (extinction, delayed inhibition, differentiation, consecutive inhibition, etc.). He also recognized supraliminal inhibition produced by extra strong stimuli. Accepting the latter, he came closely to the Wedensky unitary theory of inhibition and even borrowed some of the terms in Wedensky's vocabulary ("ultra-paradoxical stage"). However, he never fully accepted Wedensky concepts as far as conditional inhibition is concerned, first, because the theory of parabiosis cannot explain disinhibition which he described (dissolution of inhibition produced by an additional stimulus); second, because inhibition should be more developed in a tissue of lower lability according to Wedensky. And yet, Pavlovians were reluctant to accept that the cortex, this supreme leader of mental processes, has a low lability. There was a conference in Russia in April 1955 devoted to these problems. A brief account of the conference is given by Boulygin (73). The participants were divided as to whether Wedensky's parabiosis could explain all forms of central inhibition or whether other processes should be independently considered, such as, according to Orbelli and Bykov, biochemical ones. It was at this conference that Birukov disclosed his contribution showing that philogenetically conditioned excitation appears before conditioned inhibition, while Beritoff and Roitbak developed their theory of dendritic inhibition described above. Dendrites seem to save the face of both Pavlovians and Wedenskyites, offering a tissue sufficiently slow to allow the processes of inhibition to take place in the cortex.

Among the experimental problems related to conditional inhibition, the following may be mentioned (74): In conditioned dogs, all the components of a stereotype can be successively extinguished. However, in a "strong" animal, weak stimuli are more rapidly extinguished, while the opposite is observed in weak animals (parabiosis!). The author feels that in the process of extinguishing successively different components of a stereotype, a sort of training of inhibition is achieved. It must be noted that in practically all the papers of conditioning on dogs, the authors supply information as to the type of animal ("stong," "weak," "balanced," "unusually active," etc.). Correlations are found between these characteristics of the animal personality and their performance under various experimental conditions. Unfortunately, it is not always clear whether the characterization of an animal is made independently from its performance in the processes of conditioning and, therefore, whether correlation is established between two different sets of findings, or whether both express fundamentally the same thing.

Sergeev (75) found that if one "makes" a conditional inhibitor out of a neutral stimulus, an association between this inhibitor and another neutral stimulus will result in a transfer of inhibitory qualities to the second stimulus.

In men, Khanin *et al.* (76) studied inhibition of metabolic and circulatory processes under the following conditions. Subjects being trained on an ergometric bicycle were unexpectedly given a signal: "Don't start! No exercises today!" The first day the initial signal was followed by an increase of oxygen consumption and tachycardia (conditioning). The second day both metabolism and pulse showed inhibition (30 per cent decrease of metabolism).

Visceral conditioning and related problems.—A great amount of work has been done by Russian neurophysiologists in the field of interrelationships between the cortex and viscera. A general review was written by Birukov (77). Iontov (78), Ivanova (79), and Khabarova (80) describe the afferent endings respectively in the arteries, intestinal tract, and the heart. Zykina (81) revived an old observation of Claude Bernard concerning the delay of fever reactions in cases of abscesses developed in a deafferented leg. Subcutaneous injection of pyrogenic substances in such an extremity produces a generalized thermic reaction which is delayed by several hours in comparison with the controls. Conversely, if the sensory perceptions of the extremity are artificially increased, there is an early onset of fever. The author concludes that the thermic reaction to such substances is of a reflex nature. Iaroshevsky (82) shows that the leucocytosis produced by intramuscular injection of a mixture of milk and novocaine in cats produces leucopenia instead of leucocytosis which usually follows injection of milk. Leucocytosis also fails to appear after injection of milk into the deafferented extremity. Tsobkallo (83) finds that intravenous injection of a hypertonic solution of sodium chloride in a mesencephalic animal fails to produce the usual increase of blood coagulability. Brain transection at any higher level does not change normal reactions. Savinovskaia (84) showed that in normal rabbits artificial pneumoperitoneum is followed by an increase of mitoses in the mesothelial cells. In decorticated animals this reaction is not observed under the same experimental conditions. In patients with unilateral lesions of the central nervous system, vascular reflexes to thermic stimuli are asymmetrical [Shargorodsky (85)].

Subjective and objective data were analyzed by Airapetiantz *et al.* (86) following bladder distension in man. Passive distension of bladder is not associated with conscious perception or autonomic reactions unless there are reflex contractions of the bladder. Very slow distension of the bladder considerably increases its tolerance. Perception may disappear when the patient becomes adapted to a continuous distension. Perception continues to be acknowledged by the patient despite a sudden evacuation of the bladder. At the same time, prolonged or delayed respiratory, circulatory, or skin galvanic reaction may be present. A strong nonspecific stimulus may inhibit a beginning contraction of the bladder, as well as subjective and objective phenomena usually associated with such contractions. Diuresis is inhibited by bladder distension. A sham distension of the bladder in a patient accustomed to watch a manometer during such experiments may produce disagreeable perceptions and autonomic system reactions when the manometer

was falsely set above the usual threshold. Conversely, the patient may tolerate much higher degree of distension if the indication of the manometer watched by the subject is falsely set below the usual threshold. The problem of adaptation to visceral stimuli is, however, a complex one. Moussiaschikova (87) found in man and guinea pigs that skin galvanic reaction to interoceptors does not show any tendency to adaptation.

Several papers deal with the effect of activation of interoceptors upon somatic and visceral functions. Merkoulova (88, 89) found in decerebrated cats that a distension of the rectum, ileum, or bladder could elicit movements of the extremities in 15 per cent of the experiments and modify movements in 60 per cent of the cases. Hindlegs were mostly affected. Boulygin (90) found that weak interoceptive stimuli facilitate, while strong stimuli inhibit spinal reflexes. Merkoulova (91) analyzed these effects in detail, while producing in the spinal cord a "dominant focus." According to Moisseiva (92), distension of the stomach affects reflexes elicited from interoceptors to a higher degree than those elicited by stimulation of the exteroceptors. For instance, Roschina (93) found that gastric secretion is interfered with by stimulation of the rectum. This effect is suppressed by novocainization of the rectum. Sympathectomy is ineffective, while section of the spinal cord at the thoracicolumbar level suppresses these effects. After decortication the effects of the rectal stimulation upon gastric secretion are reversed. They may be conditioned in a normal animal. During experimental proctitis chronic changes in gastric secretion may occur; they are suppressed by bromides. Nikolaeva (94) showed that irritation of the intestinal tract influences contraction of the stomach. These effects are increased by strychnine and modified by decortication. Salikova (95) found modification of gastric secretion following bladder irritation. These changes are reversed by decortication and suppressed by bromides. Boulygin (96) found that the course of conditioned reflexes is modified by distension of the stomach, although the results depend upon the "type" of animal.

Is it possible to condition fundamental cellular processes? Lobashev & Sabateev (97) introduced 10 per cent alcohol in the rectum of white mice. Under such conditions, the effectiveness of vital staining is considerably increased. If injections of alcohol are preceded by auditory stimuli, these stimuli alone may enhance vital staining after only a few associations. Such conditioning may be inhibited by lack of reinforcement. However, the interpretation of these data is difficult. For instance, if alcohol increases peristaltic movements and the latter enhances vital staining, the reported results could be explained by conditioning of peristaltic movements without directly affecting the cellular processes involved in vital staining.

It was shown in the past that an increase of metabolism can be conditioned. In more recent experiments Breslov (98) attacked this problem in dogs. Inhalation of air passing through a bottle containing a piece of meat increases metabolism. The conditioned nature of this effect is suggested by the possibility of extinction of this effect. During extinction, metabolism

is depressed below the normal level. In more specific experiments, the author showed that positive alimentary stimuli increase metabolism while negative depress it. During the period of extinction, just the opposite is observed. Belenky (99) showed that changes in the white blood count, produced in dogs by sodium nucleonate injection, may be conditioned to a metronome. These changes in blood count are associated with dilation and contraction of the spleen. The experiment shows that the changes of spleen volume may be conditioned.

Topchieva (100) produced a conditioned tachycardia elicited by electrical stimulation. After a few associations previously indifferent auditory stimuli not only decrease RQ interval but also increase the amplitude of R and T waves. These changes are very difficult to extinguish in dogs. In man, premature beats can be evoked conditionally. Thus, if instead of applying pressure on the eye balls (which elicits premature beats in susceptible individuals) one just says: "I'll press on your eyes!," premature contractions occur [Peimer (101)]. Cardiovascular and respiratory conditioning could be established during acute experiments either under local anesthesia, or after the end of the general anesthesia [Koulagin (102), Kosenko (103].

Lebedev & Sevastianova (104) modified the classical experiment of Bykov. The latter found that conditional diuresis may be established in a denervated kidney. In such a case, neurohumoral conditioning through the pituitary gland is responsible for these effects. In the present experiment, the same findings are described in a kidney transplanted to the inguinal region in dogs. Positive conditioning as well as differentiation were established provided that the level of the initial diruesis is relatively low. Both positive and differential stimuli were auditory ones (ringing of bells of different pitch). Belous & Grebenkina (105) could condition diuresis by irritation of the carotid chemoceptors. Here again a neurohumoral pituitary mechanism is invoked. In more direct experiments, Endröczi *et al.* (106) show that in rats exposed to repeated stresses, pituitary-adrenocortical reactions can be conditioned to sound.

Felberbaum (107) could obtain conditioned alimentary reflexes to mechanical or thermic stimulation of the mucosa of uterus. The experiments were conducted on dogs with special care to exclude any exteroceptive stimulation. Differentiation was relatively weak. In one dog, conditioned reflexes established from one uterine tube were immediately effective following the stimulation of the tube on the opposite side.

Two general reviews on physiology of "internal analyzers" [Airapetiantz (108)] and interrelationship of the cortex and viscera [Birukov (77)] were recently published. Some additional information is found in these papers. Stimulation of baroreceptors of the renal pelvis preceding the feeding of the animals rapidly leads to the establishment of a conditioned reflex. Stimulation of the ureter 5 cm. from the renal pelvis may also be effective either by producing a generalization of the same reaction or by eliciting a differential inhibition. However, stimulation of the lower portion of the ureter is in

effective. In growing puppies the facility of forming conditioned reflexes to interoceptive stimuli (dilation of the stomach) decreases between one and three and one half months, while the opposite is found when exteroceptive stimuli (metronome) is used, so demonstrating facilitation with age. Exclusion of the visual receptors effects conditioned reflexes formed to gastric stimulation particularly in dogs of a "weak type." Simultaneous, exclusion of the visual, auditory and olfactory receptors is more effective in such cases than consecutive destruction of these receptors, leaving time for adaptation. Interoceptive reflexes are much more affected by ablation of the motor cortex than by that of the occipital cortex. However, the representation of the visceral receptors is thought to be a dynamic and diffuse one, although the anterior cortex appears to be more involved than the posterior one.

Topological studies.—Well known experiments of Shurrager and associates were repeated in Russia under the following experimental conditions. The spinal cord was sectioned in dogs at a high level. Three stimuli were applied every second to the tail of the animal. The third stimulus coincided with the stimulation of the dorsal aspect of the paw of the hindleg. Three to four thousand associations were used. An intense contraction of the semitendinosus together with an "unconditioned" motion of the tail could finally be observed when the tail alone was stimulated. However, Shamarina & Nesmeianova (109) do not feel that this phenomenon should be considered as a conditioned reflex, because several other muscle reactions could be observed as a result of these procedures (such as contractions of the semitendinosus on the opposite side or an extension of the leg on the same side). It is true that the absence of "reinforcement" decreases the amplitude of the reflex but the decreasing effect could be seen on the opposite side just as often. Also after a prolonged stimulation of the tail alone, the contraction of the tail following the stimulation of one or the other leg could be observed. This suggests to the authors that the described phenomenon is a variant of Ouchtomsky's "dominanta" [see also Nesmeianova (110)].

Complex conditioned activity established by the ordinary techniques and involving the switching of conditional stimuli was impaired by a unilateral extirpation of the superior sympathetic ganglion. It was spontaneously restored a few weeks later. However, after bilateral sympathectomy, the disturbance lasted for several months [Alexeeva (111)]. Lissák (112) found that the stimulation of the hypothalamus produces either inhibition of facilitation of the feeding conditioned reflexes. A particular stimulated point is always related to either facilitation or inhibition. The same is true for defensive conditioned reflexes. However, a hypothalamic point producing facilitation of the feeding reflex always inhibits the defensive reflex and vice versa. After formation of a conditioned reflex, stimulation of certain points of the hypothalamus without association with a conditional stimulus entirely reproduces the conditioned response. Parameters of stimulation are not critical except for the voltage [Grastyán *et al.* (113)]. Thus, stigmatic excitation of the paraventricular nucleus may elicit a conditioned running of the

cat toward the food box. The authors analyzed this behavior in two phases. The first is expressed by an orientation reflex and the second by the running toward the box. If the food box was not at that time in the visual field of the animal, the behavior elicited by the hypothalamic stimulation would be limited to the orientation reflex. They suggest that hypothalamic stimulation may produce only a facilitation of the effects of such environmental stimuli which participate in the initiation of the motor behavior. The problem remains unsolved as, even after differentiation (inhibition of noncritical environmental conditions) hypothalamic stimulation is still effective. Inhibition could be elicited from the lateral hypothalamic nuclei, the paraventricular nucleus, and also from the reticular formation.

Anokhin (114) used a technique in which the animal can be fed during reinforcements either from the right or from the left food box. In such a case, the reflexes are well adapted in a normal dog who would turn his muzzle either to the right or to the left, according to the signal. However, if areas eight to ten are ablated, the animal becomes agitated, turns his head to the right or left side ("pendular behavior") even when there is no signal. On the other hand, there is no disturbance of his salivary secretion. However, even these animals can learn the usual differential problems and, therefore, may have usual "coordination of excitatory and inhibitory processes" as far as specific stimuli are concerned. The analysis of these findings led Anokhin to believe that in conditioning there are two factors: (*a*) a general attitude of the animal in regard to the forthcoming stimuli, and (b) specific, immediate reactions to the stimuli. Ablation of the prefrontal areas effect only the behavior as far as this general attitude is concerned but does not effect specific performance. Previously, the author felt that this function of areas eight to ten cannot be explained by the classical Pavlovian concepts. He now believes that this was an unjustified criticism of Pavlov because, whatever function the frontal cortex may have, it still depends upon the "balance between the processes of excitation and inhibition".

A conditioned behavior, involving the barking of a dog, was formed by Shoustin (115). The animal was fed only when an auditory stimulus induced barking. As a result of this, the dog salivated while barking every time it perceived the conditional stimulus. In another series of experiments, the dog was trained to bark in response to the hand movements of the experimentor, being fed after ten barks. Area six was ablated after the establishment of such behavior. Conditioned barking disappeared while conditioned salivation remained. At times, barking was replaced by sneezing. Such animals were able to bark in other situations. Ablation of area eight, as well as of the temporal and parietal cortices, did not effect vocal reactions. Lagoutina (116) consistently elicited yawning in cats by stimulation of the anterior and inferior portion of the internal capsule as well as certain areas of the orbital cortex. It was found that the thresholds of these critical areas (chronically implanted electrodes were used) decrease when the animal was put under experimental conditions which would spontaneously elicit a great

number of yawns. A "decompensation" of conditioned reflexes by injury to the internal capsule was studied by Alexanian & Baklavagian (117). Motor defense reactions of a dog were formed on one side and the internal capsule injured on the opposite side. Disturbed locomotion and performance of the conditioned reflexes was only temporarily present following the operation. However, after restoration of the conditioned behavior, injection of alcohol, or to a lesser degree, strychnine produced an acute "decompensation." This suggests that regression due to additional toxic factors might reveal a latent lesion, an observation which may have clinical application.

Klosovsky & Volzhin (118) studied the effects of extirpation of the caudate nucleus in puppies at the age of two to three months. Unilateral extirpation of the caudate nucleus was not followed by any significant disturbance. Bilateral extirpation produced a severe disturbance of locomotion and stance immediately following operation (no pyramidal signs). There were alternations of hypermobility and rest. There were permanent movements when the animal was excited. While walking or running, the animals did not avoid obstacles. They were "magnetized" by any moving object or person whom they would continually follow. If, in their movement, they came to a wall, they would continue to follow along the wall and, at times, would try to squeeze in between two pieces of furniture. They would eat only when their muzzles were actually put into the food. They took into their mouths indiscriminately any object. The were hypersensitive to auditory stimuli. However, three weeks after operation, their behavior improved. They reacted to human voices. Their conditioned reflexes were still very much affected and differentiation was difficult. Autonomic functions (arterial pressure, respiration, metabolism, growth) were not affected. Many control animals were studied. Transection of thalamocaudate fibers seemed to produce the same effects. The authors concluded that the caudate nuclei contribute to the coordination of the processes of inhibition of the cortex, this action being mediated through the thalamus, at least in part.

Comparative studies.—It is in the field of comparative physiology of the higher nervous functions that the most intriguing work has been carried out in Russia during recent years. The work of Voskresenskaia & Lopatina (119) on conditioning in bees deserves admiration. All the experimental bees were marked. Tables of different color were put out in the field. Dishes containing solutions of different odors were set on the tables. Some of the dishes contained sugar syrup, others did not. The record of "visits" by individual bees to particular tables were kept. Also, the incidence of approaching a particular table by individual insects (without an actual "descent") was carefully recorded. The travel between the "home" and the table was timed. Simple "conditioning" of the bees was easy to establish and the bees collaborated in these experiments with great industry. Differentiation between the "negative" and "positive" tables was resolved. Complex stimuli consisting of a combination of a table of a particular color and a particular odor were devised. Differentiation was easier to achieve when both positive and

negative combinations were present simultaneously; more difficult when presented one after another. At times, only one trial was sufficient for a bee to make a correct differentiation during the next trip. Marked "individual differences" could be found. "Consecutive inhibition" was expressed by a prolonged duration of the round trip between the table and home. The easiest differentiation was between yellow and blue. Orange and green were not differentiated from yellow. Violet and red are barely differentiated from blue. A scale of values could be established for colors and odors according to the strength of conditioning and difficulty of inhibition. Many complex problems were presented to the bees. For instance, "switching" the significance of different colors without changing the meaning of odors and vice versa (the latter is more difficult to solve). Many bees failed to solve these problems. However, a factor complicating the experiment was revealed. Bees which never before participated in the experiment could recognize the cues without having one single trial beforehand. This ceased to happen as soon as the old bees were eliminated from the population. This observation clearly indicated some sort of inter-bee learning.

Goosselnikov (120) recorded conditioned reflexes in fish pneumatically. Unconditioned reflex movement is produced by electric shock. In young fish, a conditioned reflex was established after about 10 associations but was difficult to extinguish even after 60 "nonreinforcements" during the same day. The next day the reflex had to be re-established *de novo*. In older animals, the process of inhibition during the same day was more pronounced, but the reflexes and reactions of orientation are difficult to extinguish in certain fish. In carps, differentiation of visual stimuli does not persist for more than one day. "Consecutive inhibition" can be observed 4 to 8 minutes after application of a differential stimulus. Conditioned reflex to time interval could not be established. Generalization is difficult to overcome in reflexes originating from the lateral line in goldfish. In eels movement elicited by light or vibration of water can be extinguished by repetition, but reappears after any tactile or electrical stimulus. Extinction is difficult to produce in axolotls. Fish living on the bottom of the sea do not form a conditional reflex to light even after 345 associations, while in fish living near the surface of the sea such reflexes can be formed after only 6 to 8 associations. In frogs, inhibitory processes are weaker than in higher fish.

In pigeons [Birukov (140)] differential inhibition may be stable; consecutive inhibition does not exceed 3 minutes. Delayed inhibition and extinction are present. Delayed conditioned reflexes could be formed with a delay up to 20 seconds; they were, however, quite unstable although improving with training. In decorticated pigeons, respiratory and cardiac conditioned reflexes to inhalation of carbon dioxide could be formed; however, positive and negative stimuli were poorly differentiated. The same author reports that in wild field animals, such as foxes, differentiation may be very difficult while formation of conditioned reflexes may be achieved after only a few associations.

Knoll *et al.* (121, 122) describe two types of conditioning in rats: (*a*) an active conditioning which is nonextinguishable, and (*b*) the classical extinguishable conditioning (called recessive conditioning). If rats are put on a hot plate under a glass bell with an opening at the top, they present first disorganized movements, then a "sole-licking" behavior, then jumping movements; they finally jump to the top of the bell through an opening where they remain. Only this last phase of the behavior can be conditioned. If the training sessions are very frequent, this reflex cannot be extinguished and no form of inhibition appears during subsequent experiments, except when the animal is exhausted. As soon as the rat, placed anywhere in the laboratory, perceives the conditional stimulus, he directs himself toward the glass bell and jumps at its top. If obstacles are put in his way, he tries to avoid them and reaches the bell as long as it is materially possible. In brief, he presents fixation behavior (the authors do not use this term). In contradistinction to this technique, a recessive "extinguishable" conditioning is established when the training is performed very slowly (it may require weeks) and the exposure to heat is reduced to a minimum. With such a method, all types of conditioned inhibition, including extinction, differentiation, and secondary inhibition, were found. The authors explained the differences in the formation of either active or recessive reflexes according to the level of excitation present during training. If the level of excitation is particularly high, the reflex will be nonextinguishable and the mechanism of its formation resembles the establishment of Ouchtomsky's "dominanta."

In mice (Fedorov 123, 124) a "stereotype" could be established by alternating five positive and five negative stimuli. A "switching" is possible. (All positive stimuli will become negative and vice versa.) It is achieved after 4 to 200 trials in different animals.

Endröczi *et al.* (125) painted the tail of a female cat with valeric acid; the animal became restless, licked herself, but did not show any specific sexual behavior. After stimulation of the inlet of the vagina, the animal exhibited sham rage, performed backward snatches with her head, snarled, assumed the typical lordotic posture and made movements of copulation. If the acid was applied during the performance of a conditioned feeding reflex, the latter was blocked. Estradiol propionate exaggerated sexual responses to the combined olfactory and local stimuli as the copulation motions were then followed by leaping behavior. The animal was in a state of full orgasm and only strong exteroceptive impulses would arrest this reaction. Bilateral ovariectomy after 8 to 10 days suppressed the described behavior without effecting the conditioned feeding reflex. Progesterone failed to restore the sexual behavior in the castrated animal. However, estradiol propionate re-established completely the above described sexual behavior.

Varga (126) modified the classical technique of forming two-way conditioned connections in dogs. Feeding reflexes were formed to the electrical painful stimulus. Each time the food box appeared in the visual field of the animal, the latter would receive an electrical shock on the leg. As a result,

salivation was present each time the skin was stimulated and the animal lifted its leg during eating. This two-way reflex could be modified by changing the "excitatory state of feeding centers." Thus, if the dog was kept hungry, electrical stimulation of the leg and the sight of the food box would produce only a slight movement of the leg, while, when the dog was overfed, the dog would present a marked lifting of the leg and may not have any salivation. Conversely, the change of the intensity of the stimulating current may affect differentially defense reaction and salivation. The experiments, therefore, suggest the importance of the relationship between the functional states of the foci of excitation for the direction in which the two-way conditioning is functioning at any particular moment. Beritoff (36) discusses these findings in the light of his earlier experimental and theoretical disclusures.

A great effort has been made to compare conditioning in dogs and monkeys. Two particular parameters were tested, the one related to "mediate reflexes" and the other to delayed reactions. If two different stimuli, A and B, are associated one with the other during several experimental sessions, and then B is associated with an unconditional reflex C, the A evokes C (mediate reflex or a reflex of a second order). The possibility of forming mediate reflexes in dogs was questioned by Vysotsky & Naoumov (127). Previous positive results were explained by conditioning due to the time interval. However, Oreshouk (128) found that in some dogs mediate reflex could be established in one day. Drosdenko (129) speculates as to the mechanisms of production of such reflexes. He wonders whether the conditioned stimulus of the second order becomes directly connected to the subcortical "feeding center" or whether the connection is formed through the cortical center of the conditioned stimulus of the first order. For this purpose he establishes first a conditioned salivation to a metronome. Then he associates a picture (a black square) with the metronome. He finally obtains a conditioned response of the second order to the black square. Afterwards he suppresses the conditioned salivation to the metronome by projecting air in the ear of the animal each time the metronome is in action (with the resulting defensive reaction). However, the black squares continued to elicit salivation and no defense reaction. He concludes that there is a direct pathway between the perception of the square and the subcortical centers of salivation.

In monkeys the conditioned reflexes of second order can be easily formed. The differences are mainly in the critical time intervals separating two stimuli to be conditioned. Thus, this interval should be at least ten seconds in a dog and it may be five seconds in a monkey. If shorter, a conditioned inhibition is formed, rather than second order conditioned reflexes. These differences between dogs and monkeys are explained by the predominance of excitatory processes in monkeys and of inhibitory processes in dogs [Malinovsky (130)].

The time factors in the conditioning of monkeys was studied in different experimental situations. In one study the positive conditional stimulus was

composed of an auditory, a visual and another auditory stimuli presented for five seconds each, and separated by only .25 second. Monkeys had to squeeze a bulb and received candy for reward. A differentiation was established by replacing the middle member of this series by another visul stimulus. Conditioned reflexes were established rapidly in all animals, while during differentiation one of them broke down and became neurotic for a month. When, however, the reinforcement was delayed, differentiation could not be accomplished properly, at least not in the beginning. The monkey solved the delayed problem by approaching the bulb insidiously, waiting patiently for the last stimulus and then violently squeezing the bulb. Later in the training, differentiation could coexist with a delayed reaction [Firsov (131)]. Bolotina (132) also found that differentiation is difficult when time becomes a critical factor. For instance, conditioned reflexes to time interval are possible in monkeys but differentiation is not achieved by all animals. This kind of reflex is easier to form to a short interval and more difficult to long ones, intervals between 1 and 11 minutes being tested. In dogs, Bolotina (133) found such reflexes more difficult to establish, particularly for the shortest intervals of one to three minutes. They were facilitated if a nonspecific physical stimulus is elicited during the same interval at the beginning of the training. Kriagev (134) found that the consecutive inhibition (inhibition elicited by positive stimuli after a conditional negative stimulus) is more difficult to observe in monkeys than in dogs. The duration of such inhibitory influences depends upon the type of animal. A positive stimulus may remain positive even when it follows the negative stimulus of the same kind; for instance, clicks of the metronome at 120 per minute instead of 80 per minute. Incidentally, during the experiments on conditioning, vocalization of monkeys was recorded, each type of oscillogram being specific to a certain situation [Firsov (135)] such as a mild defensive orientation; more acute defensive reaction; when a baby monkey is taken away from its mother; when a male is abandoned by its mate; during "aggressive defense"; digestive gratification; and finally, expressing loneliness of a baby left by its mother.

In man, the conditioning associated with verbalization rasies the problem of the second signal system. In certain cases, Russian conditionalists found it rewarding to use verbal stimuli as a reinforcement of the ordinary sensory stimuli, instead of an unconditional stimulus of the classical technique. This appears to be an effective technique for conditioning and is explained by the dominant role played by speech in human behavior.

Theoretical discussion.—During the early fifties, Russian physiological periodicals carried a great number of articles directed against the "errors" of several leading neurophysiologists accusing them of doubting the all-inclusive virtue of the teachings of Pavlov. The work of Orbelli, Beritoff, Anokhin, Bernstein, as well as of Konorsky were the usual targets of the attacks directed from the advantageous position of the then all-powerful Academy of Sciences. The accused answered by explaining or confessing their "mistakes." One should hope that these distasteful discussions will only be

of historical interest. They have recently disappeared from the pages of the periodicals, partly because of the changes in the policies of a "personal cult," partly because of the pressure of new findings, particularly comparative studies, the beginning of electrophysiological exploration of conditioning, and obvious dead-ends in the studies of the second signal system. For the sake of completeness of this review, the main points of these discussions will be briefly summarized. According to Orbelli (136) there is an essential difference between the signal value of stimuli unrelated to interpersonal relationships and those implicated in such relationships. These differences should also be applied to the study of animal behavior. Orbelli considered the example when a herd leader produces a signal (for instance, a hoof beat) and produces at first a reaction of orientation in other members of the herd, followed by initiation of a specific activity. The classical laws of conditioning are not applicable to such behavior which are precursors of human verbalizations. Vatzouro & Shivanov (137) object to these comparisons, as incompatible with Pavlov's teachings. Indeed, Pavlov asserted that the second signal system is at the base of abstraction and generalization which the authors deny to the animal kingdom. Beritoff claimed that in the acquired individual behavior, two different phases should be considered: (*a*) where the total environment played a role in eliciting behavior based on personal psychonervous experience and (*b*) when specific stimuli evoked automatized responses which are the only ones which obey the classical Pavlovian laws. According to Beritoff, animal behavior may be better understood if it is not considered only as an immediate result of conditional stimuli but as a consequence of elicited, possibly nonextinguishable, mental images (for instance, the image of an opened or closed food box). His critic Vatzouro (138) asks why one would not then simply accept that mental images may be conditioned, and wonders what will remain for objective investigation of animal behavior if explanation of the latter may be attempted on the basis of subjective feelings suggested by the human introspection. Anokhin (114) recently reviewing his past "mistakes" explains that they partly stemmed from his inability to explain the behavior of the animal following the experimental crossing of extensors and flexors of the leg by tendon transfers. In such an animal, normal locomotion may be restored some time after the operation. The cartesian notion of a three-segment reflex cannot explain such an adaptive behavior. There must be mechanisms which "back signal" to the central structures of the animal that the old structure of the innervation is no longer adapted to the new circumstances. This reverse signalization is not limited to the proprioceptors, as all the receptors (tactile reception, vision, olfaction, audition, etc.) participate in informing the "centers" of the new situation. The notion of a "feed back" (the author does not use this term) must complete the concept of a three segment cartesian reflex. He called this complex system, including this additional noncartesian link, a "functional system." Originally, he did not feel that Pavlov's teachings, which accepted the cartesian notion of a three-segment reflex, could explain

this adaptive behavior of the animal. He confesses now of having overlooked the Pavlovian notion of "reinforcement" which constitutes the missing link without which the adaptive behavior cannot be explained. It is appropriate to note that another Russian neurophysiologist, Bernstein, was led to the same search for a feed-back mechanism as a result of his brilliant studies of human movements and human locomotion during the twenties and early thirties. Bernstein still held recently that the classical laws of conditioning cannot explain human motor behavior. The views of Konorsky are widely known to western investigators, and therefore will not be analyzed in this review. Shoustin (139) criticizes Konorsky's contention concerning the dependence of the the strength of conditioned processes upon the number of involved synapses because of the lack of experimental evidence of such conclusions. Beritoff (36) criticizes the contention of Astratian that a conditioned reflex may constitute an integration of an unconditioned reflex and reflex of orientation.

In general, the discussions among the Russian conditionalists can be explained by a passionate desire of some of them to assert that the teachings of Pavlov contain the necessary concepts to explain all the modalities of animal and human behavior, provided that one skillfully manipulates the general notions of excitation, induction, external and internal inhibitions, etc. The danger of dogmatic concepts which cannot be experimentally tested as to their concrete neurological mechanisms is in preventing a free development of new techniques and inquries along, as yet, unexplored lines of investigation. This danger is increased when such dogmatic claims are made from positions of political power. Despite this, however, Russian neurophysiologists have accumulated an ever-increasing amount of factual information, regardless of the theoretical approaches. The crucial importance of the impressive body of experimental findings disclosed by Pavlov and his school; their search for new theories to explain new facts; the recent introduction of electrophysiological and biochemical methods in their current investigations, and new possibilities for integration of their work with the achievements of the workers in other countries brightens the outlook for the future.

LITERATURE CITED

1. Latmanisova, L. V., *J. Physiol., U.S.S.R.*, **36**, 342–53 (1950)
2. Oushakov, B. P., Averback, M. C., Souzdalskaia, I. P., Trapina, V. P., and Cherepanova, M. N., *J. Physiol., U.S.S.R.*, **39**, 218–25 (1953)
3. Nassonov, D. N., and Rosenthal, D. L., *J. Physiol., U.S.S.R.*, **39**, 406–22, (1953)
4. Abrikosov, I. A., and Darkshevitch, V. N., *J. Physiol., U.S.S.R.*, **40**, 504–09 (1954)
5. Oufland, J. M., *J. Physiol., U.S.S.R.*, **40**, 106–14 (1954)
6. Levitina, G. A., *J. Physiol., U.S.S.R.*, **37**, 162–68 (1951)
7. Levitina, G. A., *J. Physiol., U.S.S.R.*, **39**, 167–72 (1953)
8. Miminoshvili, D. I., *J. Physiol., U.S.S.R.*, **38**, 729–33 (1952)
9. Miminoshvili, D. I., *J. Physiol., U.S.S.R.*, **39**, 226–29 (1953)
10. Danielson, A. K., *J. Physiol., U.S.S.R.*, **41**, 807–13 (1955)

11. Ermakov, N. B., and Medvedeva, N. B., *J. Physiol., U.S.S.R.*, **40,** 191–97 (1954)
12. Khrolinsky, L. G., *J. Physiol., U.S.S.R.*, **40,** 472–75 (1954)
13. Motzny, P. E., *J. Physiol., U.S.S.R.*, **36,** 133–39 (1950)
14. Popov, G. V., *J. Physiol., U.S.S.R.*, **36,** 312–19 (1950)
15. Popov, G. V., and Tzegelnitskaia, E. S., *J. Physiol., U.S.S.R.*, **39,** 199–203 (1953)
16. Sharitova, R. R., and Zhukov, E. K., *J. Physiol., U.S.S.R.*, **40,** 445–52 (1954)
17. Sorkov, F. N., *J. Physiol., U.S.S.R.*, **36,** 679–86 (1950)
18. Zirmoonskaia, E. A., *Clin. Sens. Physiol., U.S.S.R.*
19. Kostuk, P. G., *Proc. Acad. Sci., U.S.S.R.*, **105,** 858–61 (1955)
20. Rudnik, A. I., *Clin. Sens. Physiol., U.S.S.R.*, 57–70 (1949)
21. Gershouni, G. V., *J. Higher Nervous Functions*, **5,** 665–76 (1955)
22. Minute-Sorokhtina, I. P., *J. Physiol., U.S.S.R.*, **39,** 210–17 (1953)
23. Roitbak, A. I., and Cherinatvili, S. N., *J. Physiol., U.S.S.R.*, **38,** 350–55 (1952)
24. Novikova, L. A., and Khvoles, G. J., *J. Physiol., U.S.S.R.*, **39,** 34–46 (1953)
25. Vorontzov, D. S., *J. Physiol., U.S.S.R.*, **37,** 152–61 (1951)
26. Kostuk, P. G., *J. Physiol., U.S.S.R.*, **42,** 303–11 (1956)
27. Kostuk, P. G., *J. Physiol., U.S.S.R.*, **40,** 174–82 (1954)
28. Cherkess, V. A., *J. Physiol., U.S.S.R.*, **40,** 167–73 (1954)
29. Mnoukhina, R. S., *J. Physiol., U.S.S.R.*, **37,** 52–58 (1951)
30. Strakhov, A. E., and Ouspevitch, M. A., *J. Physiol., U.S.S.R.*, **36,** 140–46 (1950)
31. Goumenuk, I. G., *J. Physiol., U.S.S.R.*, **36,** 552–57 (1950)
32. Senkevich, E. V., *J. Physiol., U.S.S.R.*, **36,** 558–65 (1950)
33. Volkova, M. N., *J. Physiol., U.S.S.R.*, **37,** 422–30 (1951)
34. Volkova, M. N., *J. Physiol., U.S.S.R.*, **40,** 691–96 (1954)
35. Roitbak, A. I., *Cortical Bioelectric Phenomena* (Georgian Acad. Sci., Tbilisi, Russia, 240 pp., 1955)
36. Beritoff, S., *Beritoff Inst. Physiol. J.*, **10,** 372 (1956)
37. Roitbak, A. I., *Beritoff Inst. Physiol. J.*, **9,** 97–131 (1953)
38. Cholokashvili, E. S., and Roitbak, A. I., *Beritoff Inst. Physiol. J.*, **10,** 259–64 (1956)
39. Alexanian, A. M., *J. Physiol., U.S.S.R.*, **36,** 382–93 (1950)
40. Grastyán, E., Lissák, K., and Szábo, J., *Acta Physiol., U.S.S.R.*, **7,** 187–98 (1955)
41. Robiner, I. S., *J. Physiol., U.S.S.R.*, **40,** 404–12 (1954)
42. Gouliaev, P. I., *J. Physiol.*, **42,** 245–52 (1956)
43. Marenina, A. I., *Trudy Inst. Pavlov*, **1,** 325–38 (1952)
44. Marenina, A. I., *J. Physiol., U.S.S.R.*, **41,** 742–47 (1955)
45. Rozhansky, N. A., *J. Physiol., U.S.S.R.*, **39,** 549–60 (1953)
46. Kreindler, A., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 628–35 (1955)
47. Tzobkallo, G. I., *J. Physiol.*, **37,** 487–93 (1951)
48. Artemiev, V. V., *J. Physiol., U.S.S.R.*, **37,** 688–702 (1951)
49. Artemiev, V. V., and Babsky, E. B., *J. Physiol., U.S.S.R.*, **36,** 151–60 (1950)
50. Artemiev, V. V., and Besladnova, N. T., *Trudy Inst. Pavlov*, **1,** 228–42 (1952)
51. Roitbak, A. I., *Beritoff Physiol. Inst. J.*, **10,** 103–35 (1956)
52. Lurie, R. N., and Trofimov, L. G., *J. Physiol., U.S.S.R.*, **42,** 348–56 (1956)
53. Sakhoulina, D. T., *Proc. Acad. Sci., U.R.S.S.*, **104,** 153–56 (1955)

54. Sakhoulina, D. T., *Proc. Acad. Sci., U.R.S.S.*, **104,** 332–34 (1955)
55. Peimer, I. A., and Fadeeva, A. A., *J. Physiol., U.S.S.R.*, **42,** 319–24 (1956)
56. Rusinov, V. S., *Abstract, XIX Intern. Physiol. Congr.*, 710 (1953)
57. Naoumova, T. S., *J. Physiol., U.S.S.R.*, **42,** 361–71 (1956)
58. Novikova, L. A., and Farber, D. A., *J. Physiol., U.S.S.R.*, **42,** 341–50 (1956)
59. Lomonos, N. I., *J. Physiol., U.S.S.R.*, **39,** 27–34, (1953)
60. Lomonos, P. I., *J. Physiol., U.S.S.R.*, **40,** 566–71 (1954)
61. Fedorov, V. K., *J. Physiol., U.S.S.R.*, **36,** 513–18 (1950)
62. Fedorov, V. K., *J. Physiol., U.S.S.R.*, **42,** 173–79 (1956)
63. Lapina, I. A., *J. Physiol., U.S.S.R.*, **39,** 275–78 (1953)
64. Lapina, I. A., *J. Physiol., U.S.S.R.*, **40,** 681–83 (1954)
65. Krassousky, V. K., *Trudy Inst. Pavlov*, **1,** 143–49 (1952)
66. Alexeeva, M. S., *J. Physiol., U.S.S.R.*, **37,** 572–78 (1951)
67. Fedotov, J. P., *J. Physiol., U.S.S.R.*, **40,** 673–80 (1954)
68. Norkina, L. N., *J. Physiol., U.S.S.R.*, **36,** 524–29 (1950)
69. Kurtzin, I. T., *Trudy Inst. Pavlov*, **1,** 454–92 (1952)
70. Gambarian, L. C., *Trudy Inst. Pavlov*, **1,** 73–84 (1952)
71. Fedorov, V. K., *J. Physiol., U.S.S.R.*, **38,** 559–65 (1952)
72. Daniarov, S. B., *Trudy Inst. Pavlov*, **1,** 124–33 (1952)
73. Boulygin, I. A., *J. Physiol., U.S.S.R.*, **41,** 841–47 (1955)
74. Besnosikov, B. O., *J. Physiol., U.S.S.R.*, **40,** 653–60 (1954)
75. Sergeev, B. F., *Proc. Acad. Sci., U.S.S.R.*, **107,** 346–49 (1956)
76. Khanin, N., Krostev, K., and Iliev, I., *J. Physiol., U.S.S.R.*, **40,** 579–81 (1954)
77. Birukov, D. A., *J. Physiol., U.S.S.R.*, **42,** 142–48 (1956)
78. Iontov, A. C., *Proc. Acad. Sci., U.S.S.R.*, **105,** 172–75 (1955)
79. Ivanova, T. C., *Proc. Acad. Sci., U.S.S.R.*, **105,** 170–71 (1955)
80. Khabarova, A. J., *Proc. Acad. Sci., U.S.S.R.*, **105,** 188–91 (1955)
81. Zykina, E. S., *J. Physiol., U.S.S.R.*, **37,** 186–94 (1951)
82. Iaroshevsky, A. J., *J. Physiol., U.S.S.R.*, **37,** 69–80 (1951)
83. Tzobkallo, G. I., *J. Physiol., U.S.S.R.*, **38,** 623–32 (1952)
84. Savinovskaia, A. A., *Proc. Acad. Sci., U.S.S.R.*, **105,** 862–65 (1955)
85. Shargorodsky, L. Y., *Clin. Physiol., U.S.S.R.*, 37–50 (1949)
86. Airapetiantz, E. C., Lobanova, L. B., and Cherkashina, P. A., *Trudy Inst. Pavlov*, **1,** 14–20 (1952)
87. Moussiaschikova, S. S., *J. Physiol., U.S.S.R.*, **37,** 718–26 (1951)
88. Merkoulova, O. S., *J. Physiol., U.S.S.R.*, **36,** 470–479 (1950)
89. Merkoulova, O. S., *J. Physiol., U.S.S.R.*, **36,** 536–44 (1950)
90. Boulygin, I. A., *J. Physiol., U.S.S.R.*, **37,** 587–94 (1951)
91. Merkoulova, O. S., *J. Physiol., U.S.S.R.*, **37,** 614–20 (1951)
92. Moisseiva, N. A., *Trudy Inst. Pavlov*, **1,** 93–102 (1952)
93. Roschina, N. A., *J. Physiol., U.S.S.R.*, **37,** 598–605 (1951)
94. Nikolaeva, G. V., *J. Physiol., U.S.S.R.*, **39,** 52–59 (1953)
95. Salikova, M. V., *J. Physiol., U.S.S.R.*, **39,** 474–85 (1953)
96. Boulygin, I. A., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 732–40 (1955)
97. Lobashev, M. E., and Sabateev, V. B., *J. Physiol., U.S.S.R.*, **38,** 444–51 (1952)
98. Breslov, I. S., *Trudy Inst. Pavlov*, **1,** 116–24 (1952)
99. Belenky, G. S., *J. Physiol., U.S.S.R.*, **41,** 765–70 (1955)
100. Topchieva, E. P., *J. Physiol., U.S.S.R.*, **41,** 748–53 (1955)
101. Peimer, M. A., *J. Physiol., U.S.S.R.*, **39,** 286–92 (1953)

102. Koulagin, V. K., *J. Physiol., U.S.S.R.*, **41,** 754–59 (1955)
103. Kosenko, T. M., *J. Physiol., U.S.S.R.*, **38,** 697–701 (1952)
104. Lebedev, A. A., and Sevastianova, L. V., *J. Physiol., U.S.S.R.*, **40,** 441–44, (1954)
105. Belous, A. A., and Grebenkina, M. A., *J. Physiol., U.S.S.R.*, **39,** 591–93 (1953)
106. Endröczi, E., Lissák, K., and Szereday, Z., *Acta Physiol., U.S.S.R.*, **9,** 123–31 (1956)
107. Felberbaum, I. M., *Trudy Inst. Pavlov*, **1,** 85–92 (1952)
108. Airapetiantz, E. S., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 644–52 (1955)
109. Shamarina, N. M., and Nesmeianova, T. N., *J. Physiol., U.S.S.R.*, **39,** 601–09 (1953)
110. Nesmeianova, T. N., *Proc. Acad. Sci., U.S.S.R.*, **105,** 610–13 (1955)
111. Alexeeva, M. S., *J. Physiol., U.S.S.R.*, **38,** 593–603 (1952)
112. Lissák, K., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 636–43 (1955)
113. Grastyán, E., Lissák, K., and Kékesi, F., *Acta Physiol., U.S.S.R.*, **9,** 133–51 (1956)
114. Anokhin, P. K., *J. Physiol., U.S.S.R.*, **38,** 758–77 (1952)
115. Shoustin, N. A., *J. Physiol., U.S.S.R.*, **37,** 562–71 (1951)
116. Lagoutina, N. I., *J. Physiol., U.S.S.R.*, **40,** 23–33 (1954)
117. Alexanian, A. M., and Baklavagian, O. G., *Proc. Acad. Sci., U.S.S.R.*, **104,** 935–38 (1955)
118. Klosovsky, B. N., and Volzhin, N. S., *Problems Neurosurg., U.S.S.R.*, **20,** 8–14 (1956)
119. Voskresenskaia, A. K., and Lopatina, N. G., *Trudy Inst. Pavlov*, **1,** 141–156 (1952)
120. Goosselnikov, V. I., *J. Physiol., U.S.S.R.*, **38,** 612–18 (1952)
121. Knoll, J., Kelemen, K., and Knoll, B., *Acta Physiol., Hung.*, **8,** 327–88 (1955)
122. Knoll, J., Kelemen, K., and Knoll, B., *Acta. Physiol., Hung.*, **9,** 99–109 (1956)
123. Fedorov, V. K., *J. Physiol., U.S.S.R.*, **37,** 283–89 (1951)
124. Fedorov, V. K., *J. Physiol., U.S.S.R.*, **37,** 145–151 (1951)
125. Endröczi, E., Bata, G., and Lissák, K., *Acta Physiol., Hung.*, **9,** 153–61 (1956)
126. Varga, M. E., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 723–31 (1955)
127. Vysotsky, N. N., and Naoumov, S. F., *J. Physiol., U.S.S.R.*, **36,** 416–24 (1950)
128. Oreshouk, *Trudy Inst. Pavlov*, **1,** 166–77 (1952)
129. Drosdenko, N. P., *J. Physiol., U.S.S.R.*, **36,** 519–23 (1950)
130. Malinovsky, O. V., *Trudy Inst. Pavlov*, **1,** 205–12 (1952)
131. Firsov, L. A., *Trudy Inst. Pavlov*, **1,** 187–95 (1952)
132. Bolotina, O. P., *Trudy Inst. Pavlov*, **1,** 196–204 (1952)
133. Bolotina, O. P., *Trudy Inst. Pavlov*, **1,** 29–34 (1952)
134. Kriagev, V. J., *J. Physiol., U.S.S.R.*, **37,** 439–45 (1951)
135. Firsov, L. A., *J. Physiol., U.S.S.R.*, **40,** 18–22 (1954)
136. Orbelli, L. A., *J. Physiol., U.S.S.R.*, **36,** 5–18 (1950)
137. Vatzouro, E. G., and Shivanov, A. A., *J. Physiol., U.S.S.R.*, **37,** 528–38 (1951)
138. Vatzouro, E. G., *J. Physiol., U.S.S.R.*, **36,** 639–48 (1950)
139. Shoustin, N. A., *J. Physiol., U.S.S.R.*, **36,** 404–15 (1950)
140. Birukov, D. A., *J. Higher Nervous Functions, U.S.S.R.*, **5,** 609–18 (1955)

AUTHOR INDEX

A

Aantaa, E., 190
Aas, K., 209, 219, 220
Abajian, J., Jr., 231
Abarca, F., 244
Abbatt, J. D., 241
Abdullah, A. F., 175
Abelmann, W. H., 240
Abenavoli, G., 86
Abood, L. G , 127, 128, 132, 503
Abrahams, O., 208
Abrahams, V C., 402
Abrikosov, I. A., 558
Acheson, G. B., 125
Adamis, D., 212
Adams, C. E., 474, 475
Adams, C. W. M., 402, 468
Adams, E. C., 475
Adams, W E , 157
Adams, W. S., 216
Adamsons, K., Jr., 439, 526
Adelson, E , 96
Ades, H. W., 417, 430, 431, 433
Adey, W. R., 489-519; 399, 400, 501
Adler, L., 85, 96
Admiral, J., 135
Adolph, E. F., 61, 70, 84, 87, 89, 90
Aebi, H., 31, 51
Affeldt, J. E., 166
Affonso, O. R., 129, 134
Aggeler, P. M., 211, 212
Agress, C M , 239, 380
Aikawa, J. K., 244, 538
Aimé, L., 91, 99
Airapetiantz, E. C., 574, 576
Aird, R B., 28, 502, 503
Aisenberg, A. C., 137
Aitken, E. H., 544
Aitken, R. N. C., 477
Akametsu, O., 190
Akers, R. P., 272
Akert, K., 399, 501
Alagille, D , 209, 214
Alaimo, A., 101
Albanese, A A., 194
Albers, C., 166
Albert, A., 131, 141, 452, 454, 457, 491
Albert, R. E., 271
Albrechtsen, O. K., 176
Albright, E. C., 175
Albright, F , 457
Albright, J. F., 385
Albrink, M. J., 240, 245
Alcock, A. J W., 384
Aldous, J. G., 139
Aldridge, W N., 137
Aleksandrowicz, J., 206
Alekseyev, W. A., 282
Alella, A., 379
Alexander, B., 205, 210
Alexander, D. P., 17, 475
Alexander, F , 444, 445
Alexander, I. E., 432
Alexander, J. K., 165
Alexander, P., 132, 299, 300, 301, 303, 304, 305, 306, 307, 309, 310, 314
Alexander, R. S., 241, 242, 245, 281
Alexandrosicz, J. S., 360
Alexanian, A. M , 564, 579
Alexeeva, M S , 571, 576
Alfin-Slater, R., 305
Aliste, N., 468
Alkjaersig, N., 207, 209, 210, 214, 215, 216, 219
Allbaugh, E., 285
Allee, W. C., 59, 60
Allen, B R., 311
Allen, F. M., 308
Allen, M B., 63, 64, 75
Allen, R. D., 47
Allen, T. H., 166, 232, 233
Allende, I. L. C. de, 471, 472
Allgoth, A. M , 265
Allison, J., 245
Allison, J B., 194
Alloiteau, J. J., 404
Allwood, M. J., 258
Almeida, M. O. de, 69
Almy, T. P., 188
Alpatov, V. V., 60, 74
Alphonse, P., 520, 547
Alt, H. L., 137, 307
Altamirano, M., 20
Altland, P. D., 23
Altmann, R., 281
Alton, H. G., 209, 222
Amantea, L., 94
Amarasingham, C., 307
Amiri, H., 383
Amols, W , 407
Amour, F. E., d', 275, 410, 501
Amprino, R., 49
Ampuero, O., 468
Amram, S. S., 281, 371
Anand, B. K., 398, 399, 402, 403, 404, 502
Ancel, P., 46, 73
Andersen, B . 525
Andersen, K. F., see Faarborg-Andersen, K.,
Andersen, M., 520
Andersen, P., 496, 502, 504
Anderson, A. A., 381
Anderson, D. L , 521
Anderson, E., 403, 404, 406, 447, 467
Anderson, E. G., 191
Anderson, F. D., 492
Anderson, H. L., 126
Anderson, H. M , 530, 532, 537, 539
Anderson, S , 180, 433
Andersson, B., 401, 402, 502
Andjus, R., 88, 89, 92, 93, 96, 99
Andjus, R. K., 88, 89, 93
Andlauer, P., 83
Andre, A., 208
Andreae, E., 154
Andres, G., 44
Andrew, W , 48
Andrews, H., 307
Andrews, H. L., 311
Andrews, R. D., 17, 475
Andrews, W. H. H., 189, 265
Andy, O. J., 399, 501, 502
Angeleri, F., 501
Angelopoulos, B., 212
Annau, E., 128
Anokhim, P. K., 578
Anschutz, F , 286
Anselmi, F., 473
Anslow, W. P., Jr., 527
Anson, M. I., 74, 75
Antal, B. B., 371
Antnucci, A. J., 239, 383
Antonchak, N., 449
Apajalahti, J., 186
Applegarth, J. J., 239, 383
Aprison, M. H., 503
Apthorp, G. H., 166
Arabadjis, C , 167
Araki, T., 497
Arambarri, M. L., 478
Arana, R., 493, 499
Archer, R. K., 213
Arden, G. B , 491
Ardisson, J L., 101
Arduini, A., 501
Arends, A., 183
Arfel-Capdevielle, M., 497
Arieff, A. J , 499
Ariel, I., 92, 96
Arjona, P., 166
Armenio, S., 85
Armstrong, B. W., 156, 269
Armstrong, G. G., 281
Armstrong, H. E. O., 187
Armstrong, S. H., Jr., 240
Armstrong, W. D., 184
Arndt, T., 276
Arnott, W. M., 166

Arnould, P., 235, 407
Arnulf, G., 380
Aron, C., 97
Aron, E., 96, 97, 101, 102
Arons, I., 307
Arons, W. L., 371
Aronson, L R., 469
Arora, R. B., 370
Arpiarian, N., 314
Arrighi, M F., 27
Arrigo, L., 372
Arrington, T. R., 241
Artemiev, V. V., 567
Artz, C. P., 191, 241
Aschoff, J., 258, 286
Ash, R. W., 444
Askovitz, S. I., 286
Asmussen, E., 158, 160, 284, 378
Asper, S P , 132
Assali, N S., 544
Assenmacher, I., 400, 403, 450, 468
Åström, A., 153, 475
Athens, J. W., 233, 238
Atkinson, G., 160
Atkinson, M., 189
Atwell, R. J., 157
Auditore, G. V., 530
Auer, J., 405, 496
Auerbach, T., 246
Auerbach, V. H., 141
Augustin, E., 472, 475
Augustinsson, K.-B., 368
Austin, C. R., 474
Austin, G. M., 492, 499
Austin, J., 478
Averback, M. C., 558
Averill, R. L. W., 475
Avery, G., 51
Aviado, D. M., Jr., 153, 160, 268
Awapara, J., 139
Axelrod, J., 140
Axelrod, L. R., 130, 133
Aykut, R., 263

B

Babkin, B. P., 9, 10, 179
Babsky, E. B., 567
Bacchini, I., 102
Bachofer, C. S., 65
Bachrach, E , 60, 74, 93
Bachrach, W., 182
Bacleasse, F., 89
Bacon, R. L., 477
Bacq, Z. M., 299, 300, 303, 304, 305, 306, 307, 308, 310, 314, 362
Badawi, H. M., 471
Baddeley, R. M., 409, 476
Badoer, H., 90, 91, 374
Badenoch, J., 186
Bader, M. E., 284
Bader, R. A., 284
Badger, G. M., 132
Badre, G., 100
Baerle, R. R.-van, see Richterich-van Baerle, R.
Baez, S., 265
Bagby, D., 216
Bahl, K. N., 334
Bahnson, H. T., 155
Bahr, G. F., 472
Bailey, C. B., 264
Bailey, C. P., 85, 167
Bailey, K., 216
Bailey, O., 93
Bain, J. A., 124, 127, 128, 129
Bajusz, E., 179
Bakalvagian, O G., 579
Baker, C., 447
Baker, D. G., 89
Baker, J. M., 368
Baker, L., 311
Baker, W H., 238
Baker, W. W., 368
Bakker, J. H. J., 471
Bakst, A. A., 264
Balchum, O. J., 158
Baldini, G., 303, 305
Baldrick, F. E., 96
Baldwin, D. S., 536
Baldwin, M., 492, 496
Balestieri, A., 100
Balfour, D. C , 181
Balfour, D. C., Jr., 189
Balinsky, B. I., 43
Bálint, P., 519, 520, 545
Balke, B., 155
Ballard, W M., 48
Ballin, H. M., 94, 400
Balmain, J. H., 472
Balsac, R. H. de, 383
Baltzer, F., 43, 48
Baluev, S., 307
Ban, T., 440
Bancaud, J., 500
Bancroft, R. W., 163, 164
Bandurski, R. S., 141
Bang, F B., 407, 476
Banks, R C., 451
Bar, D. L., see Louis-Bar, D.
Barata, M. I., 383
Barbieri, L. L., 378
Barbour, H. G., 93
Barcroft, H., 255, 256, 257, 259
Bardavit, J., 410
Barger, A. C., 238, 268, 284
Bargeton, D., 89
Bargman, W., 439
Baric, J., 84
Barigozzi, C., 52
Barila. T. G., 96, 547
Barka, I., 99
Barker, S. B., 452
Barkham, P., 210
Barlow, J. C., 21, 306
Barnard, H. F., 521
Barnard, J. W., 504
Barnes, A. C., 520, 547
Barnes, D. W. H., 316, 318, 319, 320
Barnes, J. M., 15
Barnes, T. C., 61
Barnett, C. H., 517
Barnett, J. C., 492
Barnett, S. A., 84
Barowsky, H., 178
Barr, D., 239, 240
Barraclough, C. A., 403, 404, 469, 472
Barrett, W., 527
Barrnett, R. J., 84, 402, 470
Barron, D. H., 475
Barron, E. S. G., 63, 124
Barry, J., 502
Barry, S. R., 45
Barsky, J., 131
Barta, I., 440
Bartecek, A., 264
Bartelmez, G. W., 471
Bartels, H., 152, 157, 166, 268, 275, 409
Barth, L. J., 41-58; 46, 51
Bartholomew, G. A., 84, 85
Bartholomew, G. A., Jr., 84
Bartlett, M. F., 526
Bartlett, R. A., 156
Bartlett, R. G., Jr., 86, 88, 92, 96, 100
Bartlett, W., 153
Bartley, W. C., 69
Bartter, F. C., 541, 542
Baserga, A., 207
Basmajian, J. V., 496
Bass, A. D., 130
Bass, D. E., 93, 235, 236
Bassett, S. H., 271
Bassir, O., 521, 522
Bastian, J W., 471
Bata, G., 581
Bates, D. V., 151, 156
Batlle, F. F., 370
Batsel, H. L., 447
Battaglia, F. C., 475
Battey, L. L., 264
Battista, A. F., 95
Bauer, H., 182
Bauer, H. G., 458
Bauernfiend, A., 131
Bauman, A., 232, 238, 239, 245
Baumann, C. A., 524
Baumann, E. J., 456
Baumann, W., 478
Baumberger, J. P., 233
Baumgartner, G., 286
Baumgartner, J. C., 73
Bäumler, J., 51
Baxter, C. F., 314
Baxter, D. W., 406, 497
Baxter, H., 305
Baxter, J., 545
Bayley, R. H., 371
Baylin, G. J., 185
Baylis, J. H., 177
Bayliss, L. E., 374
Beach, F. A., 404, 405, 469

Beaconsfield, P., 257
Beadle, L. C., 329–58: 337 338, 339, 340, 341, 342, 344, 352, 353
Beadle, S. F., 342
Beals, R., 153
Beament, J. W., 71
Beamer, P. R., 74
Beard, R. L., 364
Bearden, H. J., 468
Beaton, J. R., 133
Beattie, J., 96, 97
Beaumariage, M., 303. 306. 307, 308
Beaumont, J. L., 210, 219
Becerra, M., 468
Beck, E. M., 93, 96
Beck, H., 408
Beck, J. C., 246, 541
Beck, L., 377
Becker, E. L , 155, 283, 384
Becker, J., 306
Becker, R. A , 28
Beckett, S B., 126
Becquerel, P., 67, 68
Bedell, G. N., 165, 192
Bedford, P. D., 186
Beer, R., 268
Behmann, F. W., 88
Behnke, A. R., 163
Behrman, S. J., 470
Beidler, L. M., 491
Beigelman, P. M., 449
Bein, H. J., 401
Békés, M., 179
Bekesy, G. von, 417, 418, 419, 420, 422, 423, 424, 425, 426, 427, 429, 434
Bekker, J. M., 360
Bekkum, D. W. van, 301, 302
Belcher, E. H., 314
Belcourt, J., 360
Bělehradek, J., 59–82; 59, 60, 61, 62, 64, 66, 68, 69, 75
Belenkij, G. S., 276
Belenky, G. S., 575
Bell, A. L. L., Jr., 154
Bell, F. K., 384
Bell, F. R., 407
Bell, L. G., 182
Bell, W. N., 209, 213, 222.
Bella, D. D., see Della-Bella, D.
Bellairs, R., 44
Bellemare, E. R., 360
Beller, F. K., 213
Bellet, S., 369, 372
Beloff-Chain, A., 17
Belous, A. A., 576
Belval, H., 71
Ben, M., 447
Bender, M. B., 492, 497
Benedict, F. G., 83
Benelli, C., 284
Benetato, G., 405
Benfey, B. G., 450, 468
Benichoux, R., 380
Benirschke, K., 478
Benitez, D , 138
Benitte. A., 100, 101
Benjamin, A. D., 524
Bennati, D., 265
Bennett, D R., 123, 124
Bennett, I. L., Jr., 188
Bennett, L. R., 309
Benoit, J., 400, 403, 450, 468
Benoit, O., 94
Benson, E. S., 365
Benson, G. K., 468, 476
Benson, J. A., Jr., 184, 185, 270
Benson, R. W., 433
Benstead, N., 237
Benstz, W., 100
Bensuson, H. B., 134
Benthe, H. F., 74, 372
Benton, A. L., 499
Benton, D. A., 194
Ber, E. M., see Michel-Ber, E.
Berard, E., 101, 490, 500
Bercel, N. A., 502
Berentdt, 101
Berg, W. E., 50
Bergen, J. R., 444
Berger, G. P. v., 101
Berger, J., 471, 476
Berger, N. E. K., see Krijgsman-Berger, N. E.
Berger, R. E., 132
Bergh, F., 66
Berglund, E., 158, 376, 379, 380
Berglund, F., 536, 540
Bergmann, F., 134
Bergna, L. J., 222
Bergner, A. D., 135
Bergsagel, D. E., 221
Bergstrand, A., 99
Bergström, J., 262
Beritoff, S., 564, 582, 585
Berkel, H. A., 368
Berkowitz, S. D., 45
Berlin, L., 497
Berlin, N. I., 231, 233, 234, 236, 237, 238, 239, 242
Berliner, R. W., 526, 533, 534, 535, 547
Berman, A J., 500
Berman, D. A., 125, 379
Berman, H. J., 526
Berman, M. D., 24, 25
Bernard, C., 88
Bernard, I., 474
Bernard, J., 207
Berne, R. M., 90, 263
Bernéus, B., 164
Bernhard, M., 48
Bernhard, W. F., 97, 189, 445
Bernheim, F., 132
Bernsohn, J., 127
Bernstein, S E., 188
Berr, M., 86
Berry, A. M., 372
Berry, C. M., 492
Berry, M. M., 453
Berson, S. A., 231, 232, 233, 238, 245
Bertalanffy, L. von, 19
Bertelli, A., 123
Berthaux, P., 372
Berti, T., 100
Bertrand, C., 499
Berzelius, J. J., 7
Besladnova, N. T , 567
Besnosikov, B. O., 573
Bessis, M., 207
Best, A. T., 83
Best, J. B., 63
Bethell, F H., 311
Bettelheim, F. R., 216
Betz, E. H., 305, 306, 316
Betz, H., 303, 305, 306, 307, 308
Bever, A. T., 473
Bezzi, E., 101
Bhargava, K. P., 401
Biagio, F. di, 492
Bickford, R. G., 501
Bidwell, E., 211
Biemond, A., 494
Biesele, J. J., 132
Biezunski, N., 216
Bigelow, F. S., 208
Bigelow, W. G., 85, 86, 87, 90, 91, 92, 93, 100
Bigger, L. C., 29
Biggers, J. D., 472
Biggs, R., 209, 220, 221
Bilger, R. C , 433
Billig, D. M., 160, 268
Billingham, R. E., 65, 67
Billings, H. H., 234
Bilski-Pasquier, G., 218, 219
Binder, M. J., 239
Bine, R. Jr., 189
Binet, L., 86, 90, 273, 364
Binet, P., 86
Bing, R. J., 90, 91, 122, 125, 365, 367, 374
Bingeman, M. E., 305
Binhammer, R. T., 309, 313, 314, 318
Binkley, S. B., 131
Binns, V., 132
Biörck, G., 86, 91, 373
Birbeck, M. S. C., 476
Bird, G. S., 236
Birke, C., 444
Biroli, G. P., Pirzio-Biroli, G.
Birukov, D. A., 574, 576, 580
Birzis, L., 404, 496, 502
Bishop, G. H , 494
Bishop, J. M., 189, 284, 378
Bisteni, A., 93, 370
Bittner, J. J., 468
Björk, V. O., 157, 376
Björkman, S., 159
Bjurstedt, H., 151–74:
Black, D. A. K., 530,531

Black, L., 49
Black, S. P. W., 281
Black, V. S., 346
Blackburn, C. R. B., 185
Blackburn, H. W., 371
Blades, B., 86
Bladier, B., 371
Blahd, W. H., 240, 245
Blain, J. M., 125, 367
Blair, J. R , 89
Blake, W. D , 520, 543, 547
Blakeley, E. R., 140
Blakemore, W. S., 156, 159
Blandau, R. J , 472
Blasius, R., 473
Blatt, M. H. G., 449
Bleehen, N. M., 187
Blicharski, J., 206
Blinks, L. R., 60
Bliss, E. L., 444
Bloch, E., 444, 478
Bloch, E. H., 270, 282
Bloch, H., 70
Blomstrand, R., 185
Blondheim, S. H., 189
Blood, F. R., 186, 275, 410
Bloodworth, J. M. B., 457
Bloom, G., 206
Bloom, W. L., 261, 283, 367
Bloomfield, B., 366
Blos, P., 91
Blount, H. C., Jr., 307
Blount, S. G., Jr., 85, 158
Bluemle, D. B., 166, 167
Blum, F., 97
Blum, H. F , 51
Blum, J., 384
Blum, J. J., 124
Blum, R. H., 500
Blumenfeld, S., 91
Blumenthal, M. R., 524
Blumgards, L., 190
Boag, L. M., 236
Bobb, J R. R., 238
Bobbio, A., 101
Boccabella, A., 132
Boccabella, R., 132
Bock, K. D., 255, 259
Bodenstein, D., 51
Bodian, D., 407
Bodiou, J , 101
Boell, E. J., 45, 503
Boerema, I. A., 86
Boernstein, W. S., 490
Bogardus, G. N., 285, 375
Bogdanove, E. M , 403, 442, 454, 455, 468
Bogen, H J., 71, 74, 75
Bogin, M., 443
Bogoroch, R , 452
Bogucki, M., 334
Bohr, D. F., 270, 272, 311
Bohr, V. C., 86, 88
Boissier, J. R., 372
Boistel, J., 92, 100, 370
Boiteau, H., 90
Boivin, J. M , 211
Bolene-Williams, C., 263, 379
Boley, J. O., 184
Bollman, J. L., 184, 185, 270
Bölönyi, F., 440
Bolotina, O. P., 583
Bolt, W., 157, 159, 269
Bond, V. P., 299-328; 178, 299, 300, 306, 308, 309, 310, 312, 314, 315, 316, 317, 318
Bondurant, J. H., 232
Bondurant, S., 283
Bone, G., 340
Bonet-Maury, P., 307
Boniface, K. J., 383
Bonner, J., 141
Bonner, J.T., 50
Bonnet, V., 497
Bonnin, J.A., 220
Bonte, F.J., 189
Bonvallet, M., 86,100
Booj, H.L., 61
Boot, L.M., 469
Booz, G., 316
Borduas, J.L., 371
Borei, H., 348
Borell, U., 472, 473
Borelli, J., 208
Borges, S., 383
Borghgraef, R.R.M., 538
Borison, H.L., 401
Borman, A., 449
Born, G.V.R., 22, 136, 155, 166, 383
Bornschein, H., 434
Bornstein, J., 22
Borun, E.R., 525, 526, 537
Bosch, J.J. van der Werff ten, 409, 458, 469
Boshes, B., 499
Bosma, J.F., 499
Bosniak, M.A., 132
Boss, J., 275
Bostroem, B., 161, 268
Bostroem, H., 137
Botelho, S.Y., 165
Bottelier, H.P, 60
Botts, J., 124
Boucot, N.G., 156
Bouhuys, A., 157
Boulygin, I.A., 573, 575
Bounameaux, Y., 207, 208
Bound, J.P., 190
Boussemart, E., 474
Bovet, D., 101, 281
Boving, B.G., 475
Bowditch, S.C., 502
Bowen, E.H., 246, 520
Bowers, D., 158, 285, 374, 375
Bowers, J.Z., 184
Bowman, E.M., 135
Bowman, H., 84
Bowman, H.C., 236
Boyce, W.H., 523, 536
Boyd, L.J., 183
Boyd, R.S., 184
Boyer, P.D., 28, 140
Boyesen, S., 504
Boyle, D., 194, 195, 452
Braasch, J.W., 178
Brace, K.C., 23
Brachet, J., 48, 69
Brackney, E.L., 192
Bradley, B., 233, 234
Bradley, S.A., 241
Bradley, S.E., 513-56: 267, 513
Bradley, S.G., 50
Bradner, W.T., 188
Brady, J.V., 400, 502
Brady, L.W., 232, 233
Brady, R.O., 138
Bragdon, J.H., 218
Brain, R., 504
Brambel, C.E., 218
Brambell, F.W.R., 475
Brancadoro, G., 101
Branch, C.H.H., 444
Brand, T. von, 60
Brandfonbrener, M., 284, 383
Brandlin, F.R., 277, 373
Brandon, A., 405, 503
Brandt, J.L., 188
Brannan, W.M., 219
Brannick, L.J., 403, 447, 527
Braude, R., 188
Brauer, R.W., 130
Braun, W., 30
Braunstein, J.R., 375
Braunsteiner, H., 206, 207
Braunwald, E., 281, 284, 371, 527
Braveny, P., 91, 92
Brazda, F. G., 128
Brazell, E., 231
Brazier, M.A.B., 400
Brecher, G., 299, 300, 302, 309, 310, 314, 316
Brecher, G.A., 159, 374
Brecher, G.R., 287
Breckenridge, C., 101
Breder, C.M., 346
Breemen, V.L. van, 441, 468
Breese, S., 233
Brehm, H., 283
Breiter, E., 276
Bremer, F., 69, 72, 433
Brendel, W., 100, 166
Breneman, W.R., 473
Brennan, J.F., 504
Brenner-Holzach, O., 28
Bresler, E.H., 519
Breslov, I.S., 575
Brettschneider, H., 440
Breuer, H., 473
Breuninger, H., 101
Brewer, G., 93
Brewin, E.G., 91, 92, 154
Brewster, W.R., 85, 92, 93
Bricaud, H., 383
Brickner, E.W., 266
Bridgewater, A.B., 181
Brierley, J.B., 44, 127, 128
Brieter, E., 405

Briggs, F. N., 403, 439, 443, 448, 449, 451, 469
Briggs, R., 48
Brigham, J. C., 93
Bright, E. M., 97
Bright, R. H., 520, 547
Brill, I. C., 370
Briller, S. A., 371
Brilmayer, H., 100, 127
Brimblecombe, R. W., 96
Brind, S. H., 260, 277, 373
Brindley, G. S., 491
Brinkhous, K. M., 211, 219
Briscoe, W. A., 156
Britton, S. W., 93, 97
Brizzee, K. R., 453
Brobeck, J. R., 403, 449, 450
Brockman, H. L., 89
Brockhoff, F. G., see Grosse-Brockhoff, F.
Brod, J., 8, 520
Broda, E. F., 64
Brodal, A., 406, 493, 499
Brodie, B. B., 133, 140, 503
Brodish, A., 445
Brodsky, W. A., 16, 533
Brody, J. I., 369
Brody, T. M., 124, 127, 137
Broekhuysen, L., 86
Brogan, F. A., 423, 426
Brohult, A., 305, 306
Broida, H. P., 239, 281, 377
Brombacher, W. G., 286
Bromiley, R. B., 430
Bronson, L. H., 70
Brooks, C. McC., 91, 95, 154, 492
Brooks, D. C., 492
Brooks, L., 233
Brooks, S. C., 32
Brostoff, P., 268, 283, 378
Broustet, P., 383
Browman, L. G., 470
Brown, A. W. A., 364
Brown, D. D., see Denny-Brown, D.
Brown, D. E., 73
Brown, D. E. S., 62, 73
Brown, E., 231-54; 231, 232, 233, 234, 238, 240, 244
Brown, E. B., Jr., 234, 283, 369
Brown, F. K., 277
Brown, G. B., 132
Brown, G. L., 490
Brown, G. M., 236
Brown, J. B., 476
Brown, J. F., 263
Brown, J. F., Jr., 133
Brown, J. M., 383
Brown, J. R. C., 318
Brown, M., 499
Brown, M. B., 310, 315, 317, 318, 319
Brown, M. G., 63
Brown, P., 69
Brown, P S , 471
Brown, R. V., 274
Brown, T G., 362
Brown, W M. C., see Court-Brown, W. M.
Browne, J. S. L., 246
Browne, K. M., 502
Browner, W. J., 154
Brown-Grant, K., 452, 453, 454, 471. 476
Bruce, E. J., 166
Brues, A. M., 306
Brull, L., 262, 519, 536, 545
Brummer, P., 182
Brun, C., 262, 515, 516
Brunaud, M., 85
Bruns, F., 130
Brust, A. A., 261
Bryan, J. H. D., 477
Bryant, S. H., 19, 20, 490
Bubnoff, M. von, 30, 383
Buchanan, D. J., 307
Buchard, F., 101
Buchem, F. S P. van, 269
Bucht, H., 262
Buchthal, F., 499
Buckley, N. M., 267, 270
Bucy, P. C., 501
Budde, H., 152, 275, 409
Budolfsen, S. E., 184
Bueding, E., 121
Buffoni, N. F., 123
Bugaievsky, M. F., 66
Bühlmann, A., 151, 155
Bülbring, E., 22, 137
Bullock, T. H., 359
Bullough, W. S., 473
Bunch, L. D., 477
Bunge, R. G., 67
Bunin, K. W., 284
Buondonno, E., 101
Burbridge, T. W., 127
Burch, G., 23
Burch, G. E., 239, 242, 245, 258
Burchell, H. B., 372
Burdick, F. H., 307
Burgen, A. S. V., 176
Burger, H. C., 285
Burger, J. W., 364
Burian, R., 348
Burke, A. W., Jr., 306
Burke, D., 134
Burke, J. D , 241
Burkl, W., 471
Burks, R., 450
Burlington, H., 519, 545
Burn, J. H., 368, 377
Burnham, S. M., 194
Burnett, C H., 244
Burnett, W. A., 164
Burnett, W. T., Jr., 301, 302, 305, 308
Burns, H. L., 89
Burstein, M., 217, 218, 273
Burton, A. C., 61, 85, 86, 95, 245, 259, 271
Burton, S. D., 189
Burwell, C. S., 236, 237, 475
Burwell, R G., 520
Bury, J. D., 237, 271
Busch, H., 138
Busch, W., 384
Buser, P., 399
Bush, J. A., 234
Bush, L. F., 469
Bush, S., 307
Bush, V., 1
Buskirk, E. R., 97
Bussan, R., 369, 370
Butler, E. G., 51
Butler, J., 166
Butler, J. A. V., 300
Butler, T. C., 126
Butt, W. R., 471
Butzengeiger, K. H., 244
Buu-Hoi, N. P., 305, 307
Byers, S. O., 186, 189, 192
Byham, C. L., 433
Byrnes, W. W., 469
Byron, M. C., 443

C

Cabanes, T. F., see Feyel-Cabanes, T.
Cachera, R., 239, 240
Cadilhac, J., 399
Caen, J., 207
Cafruny, E. J., 130, 538
Cahane, M., 455
Cahane, T., 455
Cahill, G., Jr., 527, 542, 543
Cahn, J., 87, 91, 97, 100, 101, 102, 445
Cahn, T., 475
Caiger, P., 366
Caileau, R., 132
Cain, J. C., 190
Cajal, S. R. y, see Ramon y Cajal, S.
Caldwell, P. C., 17, 21
Calkins, E., 14, 93
Callaghan, J. C., 86, 92, 93
Callamand, O., 347
Callow, A. D., 191
Calloway, N. O., 457
Camera, A., 212
Camosso, M., 49
Campbell, A. M., 457
Campbell, E. H., 94
Campbell, E. J., 166
Campbell, E. J. M., 499
Campbell, E. W., 207
Campbell, F. W., 85
Campbell, H. J., 446
Campbell, J. B., 504
Campbell, L. A., 381
Campeti, F., 263
Canada, W. H., 178
Canaveri, A. A. M., 222
Cane, V., 491, 502
Canivenc, R., 475
Cannon, J. F., 526
Cannon, W. B., 97
Cantarow, A., 87, 452

Capaldo, A., 208
Capdevielle, M. A., see Arfel-Capdevielle, M.
Capeci, N. E., 154, 524, 537, 539
Capon, A., 278
Capone, V. A., 218
Capraro, V , 60, 140
Cara, M., 151, 165
Carballeira, A., 541
Carbone, J V., 242
Cardeza, A. F., 475
Cardi, L., 166
Cardot, J., 361, 364
Cardozo, E. L., 240
Carey, M., 14, 15, 20
Carlens, E , 159
Carli, F. de, 95
Carlill, S. D., 269
Carlisle, D. B., 361, 363
Carlo, J., 475
Carlsen, E., 22
Carlson, L. D., 89
Carlson, W. W., 513
Carlston, A., 164
Carmela, A., 50
Carmichael, H. T., 455
Carnelly, H. L., 70
Carnot, M. C., see Coquoin-Carnot, M.
Carpi, A., 262
Carr, C. J., 384
Carr, T. L., 457
Carrano, F., 50
Carreras, M., 501
Carroll, D. G., 156
Carson, N. A. J., 207
Carter, F., 470
Carter, J. R., 214
Carter, M. K., 140
Carter, R. E., 308
Carterette, E. C., 433
Carton, E., 26
Cartwright, G. E., 234
Casby, J. U., 432
Cascio, G., 132
Case, R. B., 379, 380
Casper, A. G. T., 541
Cassles, D. E., 381
Cassidy, G. J., 86, 97, 98
Castaing, R., 383
Casten G. G., 366
Castillo, J. del, 370, 371
Castle, E J., 192
Castle, W. B., 71, 72, 183
Castleman, L., 188
Catanzaro, R., 17
Cate, J. T., see Ten Cate, J.
Cathala, H. P., 85, 100
Cathcart, E. S., 245
Cattell, McK., 370
Cauna, N., 490
Causey, G., 490
Cavanaugh, D. J., 136
Cavanaugh, M. W., 44, 385
Cavert, H. M., 140
Cayer, D., 240
Cazorla, A. T., 283
Cazorla, T. A., 235
Cazzullo, C L., 94, 101
Cedard, L., 476
Celander, H., 163
Century, B., 127
Cerletti, A., 100, 122, 262, 372, 273, 379
Cervoni, P., 409, 472
César Merino, M., 233
Cessay, C. V., see Vieille-Cessay, C.
Chadwick, I. E., 59
Chaet, A. B., 48
Chaikoff, I. L., 189, 245, 442
Chain, E. B., 17
Chalmers, T. M., 542
Chamberlain, J. L., 51
Chambers, E. L., 32
Chambers, R., 32
Chambers, R. D., 96, 97
Chambers, W. W., 493, 496
Chambon, Y., 469, 475
Chance, M. R. A., 127, 128, 471
Chandler, G. N , 185
Chanel, J., 99
Chang, C., 233
Chang, H. T., 495
Chang, S. L., 70
Chapin, J. L., 153, 162, 166
Chaplin, H.,Jr., 60, 62, 74, 232, 240, 241
Chapman, L. F., 433, 501
Chapman, R. F., 60
Chapman, W. H., 299, 300, 302, 309
Chapman, W. P., 400
Chappell, J. B., 136
Chardon, G., 92, 94, 100, 101, 277, 407
Charleson, D. A., 88, 90
Charlier, R., 303, 306, 307, 308, 370
Charney, C. W., 477
Chart, J. J , 439, 541
Chastain, S. M., 309
Chatelin, C. L , 85
Chatfield, P. O., 84, 92, 94, 95, 503
Chatonnet, J., 86, 87, 100
Chatterjea, J. B., 208
Chauchard, P., 85, 94, 95, 100, 405
Chaves, N., 360
Chavré, V. J., 32, 135, 179
Cheek, D. B., 543
Cheek, W. R., 450
Chen, K. K., 124
Chen, K. P., 233
Chen, P. S., 30, 43
Chen, T. T., 476
Cheng, A. L., 305
Cheng, C. P., 449
Cheng, D. W., 449
Chenoweth, M. B., 121-50; 123, 127, 131, 138, 140
Cherepanova, M. N., 558
Cherinativili, S. M., 561
Cherkashina, P. A., 574
Cherkess, V. A., 562
Cherniack, R. M., 165, 269
Cherry, R. B., 166, 432
Cherry, W. B., 70
Cheval, M., 475
Chevallier, P., 218, 219
Chevillard, L., 91, 379
Cheymol, J., 102, 449
Chidsey, C., 241, 267
Child, G. C., 239, 240
Childs, A. W., 266, 515, 524
Chinard, F. P., 29, 240, 270, 515,522, 524
Chinn, H. I., 166
Chipley, P. L., 281
Chiquoine, A. D., 50
Chodos, R. B., 238
Cholokashvili, E. S., 564
Chow, B. F., 183
Chow, K. L., 500, 501
Christensen, E., 500
Christensen, H. N., 28
Christenson, W. R., 303, 314
Christie, R. V., 151
Christo, E., 457
Christophersen, A. R., 92
Christophersen, J., 50, 59, 73 74, 75, 85
Church, G., 50
Churchill-Davidson, H. C., 87, 90, 91, 242
Churchill- Davidson, I., 162
Chusid, J. G., 500
Chytil, M., 516
Cicardo, V. H., 276, 405
Cier, J. F., 90, 92
Citterio, P., 45
Cizek, L. J., 232
Clare, M. H., 494
Claringbold, P. J., 472
Clark, A. M., 302, 308
Clark, C. T., 133
Clark, E. C., 176, 491
Clark, G. M., 125
Clark, J. K., 153
Clark, J. T., Jr., 232
Clark, J. W., 301, 308
Clark, M. L., 181
Clark, W. G., 239, 380
Clarke, E., 529, 531
Clarke, E. W., 140
Clarke, M., 132
Clarkson, E. M., 22
Clatanoff, D. V., 183
Claus, A., 341
Clausen, D. F., 233, 285
Claxton, E. B., 207
Clay, M., 311
Cleghorn, R. A., 439, 444, 468, 495, 502
Clejan, L., 369
Clemedson, C.-J., 163, 164
Clement, F. L., 159, 374
Clemente, C. D., 407, 492

Clemmons, J. J., 472
Clerc, N. A., 490
Clermont, Y., 476
Clifton, K. H., 470
Cline, F., Jr., 157
Clowes, G. H. A., 132
Clugston, H., 304, 305
Coalson, R., 478
Coates, M. E., 188
Coats, D. A., 176
Cobb, D. M., 343
Cobbold, A. F., 255, 256, 260
Cochran, G. W., 523, 536
Cochran, K. W., 134
Cochrane, L. S. G., 127
Cochrane, W., 517
Code, C. F., 177, 180, 184, 410
Coelho, E., 383
Cogswell, R. C., Jr., 154
Cohen, A., 161
Cohen, A. I., 45
Cohen, A. K., 220
Cohen, G., 156
Cohen, J. A., 232, 301, 302
Cohen, J. J., 540
Cohen, L., 307
Cohen, L. A., 490
Cohen, A. I., 45
Cohen, M. J., 491
Cohen, M. L., 490
Cohen, S., 49
Cohn, J. E., 156
Cohn, M., 136
Cohn, T. D., 187
Coignet, J., 85
Cole, J. W., 189
Cole, L. J., 308, 310, 312, 313, 315, 316, 317, 319, 320
Cole, R. D., 476
Cole, W. H., 333, 338
Cole, W. V., 499
Coleman, D. H., 243, 246
Colenhofen, K., 259
Coleridge, J. C. G., 372
Coles, D R., 257, 258
Colfer, H. F , 455
Collander, R., 63
Collet, A., 166
Collier, C. R., 166
Colodzin, M., 233
Colopy, J. E., 212
Colpron, G., 210
Colwin, A. L., 47
Colwin, L. H., 47
Comarr, A. E., 411
Combes, B., 266, 515
Combrisson, A., 93
Comét, S., 161, 285
Cominsky, B., 524
Comnene, J. S. de, 371
Comolli, R , 49
Comroe, J. H., Jr., 165
Comsa, J., 307, 308
Conard, R. A., 299, 300, 302, 309
Conden, J. O., 191
Condon, G. P., 475
Condon, H. M., 66
Congdon, C. C., 310, 316
Congdon, C. L., 312
Conger, A. D., 308
Conley, C. L., 209
Conly, S., 191
Conn, H. L., Jr., 371
Conn, J. W., 439, 452
Conner, E., 264
Conner, E. H., 242, 272
Consolazio, C. F., 270
Conti, C., 477
Contopoulos, A. N., 243, 244
Conway, E. J., 14, 15, 20, 26, 27
Cook, C. D., 166
Cook E. F., 64
Cook, J., 217
Cook, M., 366
Cook, O. S., 86
Cook, S. F., 47
Cooke, R. E., 187
Cookson, B. A., 85, 90, 373
Cooley, C. A., 89
Cooley, S. L., 135
Coombes, J. S., 25, 498
Coombs, C. J. F., 477
Coon, M. J., 195
Coon, R. W., 220, 221
Cooper, C., 133
Cooper, D. Y., 232, 233
Cooper, I. S., 264
Cooper, J. A. D., 137, 307
Cooper, J. R., 140
Cooper, K. E., 256, 275
Cooper, M., 231
Cooper, P., 167
Cooper, P. D., 138
Cooper, R. G., 283
Cooper, S., 491, 492
Cooper, T., 209
Cooper, W. G., 366
Copeland, D. E., 346
Copenhaver, W. M., 47
Copley, A. L., 208
Coquoin-Carnot, M., 472
Coraboeuf, E., 86, 92, 100, 370
Corbascio, A. N., 286
Corcoran, A. C., 527, 542
Corda, M., 364
Cordero Funes, J. R., 407
Cordier, D., 99
Cormack, R. S., 153
Cornec, A. R., see Renier-Cornec, A.
Corner, G. W., Jr., 472
Cornfield, J., 194, 541
Cornman, I., 132
Correa Freire, J. R., 475
Corrigio, J. G., 186
Corteggiani, E., 408
Corcilain, J., 457
Corwin, A. H., 218
Cosimano, S. J., 383
Cosimano, S. J., Jr., 267
Cosnier, J., 101
Costello, M. J., 305
Cotten, M. deV., 376
Cotter, G. J., 305, 307
Cottier, P. T., 547
Cottin, D., 383
Coulson, R. A., 533, 535
Coulter, E. P., 305
Counce, S. J., 46
Courbier, R., 85, 86, 88, 91
Cournand, A., 154, 268
Cournand, M., 377
Courrier, R , 98, 102
Court-Brown, W. M., 305
Courtois, G., 127
Courtoy, P., 268
Courvoisier, S., 100
Cousons, S F., 300, 303, 304, 305, 306, 307
Coussens, R., 133
Covasneanu, Z., 369
Covel, W. P., 421
Covian, M. R., 276, 407
Covino, B. G., 88, 90, 373
Cowan, W. M., 398, 493
Cowie, A. T., 470, 476
Cowie, D. B., 29,
Cox, B. J., 176
Cox, C. P., 476
Cox, F. W., 210
Coxon, R. V., 166
Coye, R. D., Jr., 524
Coyne, B. A., 28
Crabbe, J., 444
Craddock, D. G., 216
Crafts, R. C., 244
Cragg, B. G., 399, 501, 502
Cragg, J. B., 337, 338, 352
Crain, J. C., see Cymerman-Craig, J.
Craig, J. M., 527
Craig, R. L., 381
Crane, W. A. J., 180
Cranston, W. I., 90, 92
Crawford, J. D., 522, 527
Crawford, J. M., 475
Cree, E., 157
Creese, R., 14, 20
Crelin, E. S., 474
Cremer, J. E., 137
Crepax, P., 126
Creutzberg, F., 475
Creutzfeldt, O., 85
Crewdson, F., 190
Crismon, J. M., 91, 92, 93, 272
Critchlow, B. V., 467-88; 403, 469
Crone, C., 262, 515, 516
Cronkite, E. P., 299-328; 207, 299, 300, 302, 306, 309, 310, 314, 316
Cronwich, J., 23
Crooke, A. C., 457
Cross, B. A., 502
Cross, F. S., 192
Cross, K. R., 192

Cross, R. J , 131
Crosskey, M., 499
Crossman, E. B., 73, 74
Crowe, P. J., 185
Crowell, J. W., 283
Crowley, W. P., 285
Croxatto, H., 468
Crumpton, C. W., 263, 380
Cruz, A. da, 100
Cruz, J. M., 265
Csapo, A., 475
Cucci, C. E., 375
Cuénod, C. L., 154
Cuker, R., 456
Cull, T. E., 287
Cullen, C., 489, 495
Cullen, C. F., 242
Cullum, L. E., 167
Cummings, G., 378
Cummins, A. J., 185
Cummins, J. F., 179
Cunningham, A. W. B., 309
Cunningham, D. J. C., 153
Curri, S., 403, 451
Curri, S. B., 402
Currie, A. R., 442
Curry, C. F., 166
Curry, J. H., Jr., 384
Curry, M. F., 46
Curtis, G. W., 189
Curtis, J. K., 157
Curtis, R. H., 541, 542
Cuypers, Y., 536
Cymerman-Craig, J., 132
Czerski, P., 207

D

da Cruz, A., see Cruz, A. da
Dagg, C. P., 46
Dagliesh, C. E., 133
Dahlback, O., 286
Dailey, R. E., 184
Dailey, U. J., 179
Dainty, J., 24
Daitz, H. M., 398
Dalcq, A. M., 47
Dale, W. A., 155, 167
Dalle Ore, G., 400, 502
Daly, I. deBurgh, 268
Daly, M. deBurgh, 160, 269
Dam, H., 210
Damann, R., 87
Damaria, W. J. A., 521
Damashek, W., 208
D'Amato, H. E., 90, 93, 236
Damgaard, E., 313
Damgaard-Nielsen, M., 86
Dammin, G. J., 545
d'Amour, F. E., see Amour, F. E., d'
Dancis, J , 475
Danes, B. S., 46
d'Angelo, S. A., 87, 452
Danhof, I., 519
Daniarov, S. B., 572
Daniel, P. M., 440, 491, 492
Danielli, J. F., 48, 63
Danielson, A. K., 559
Danon, M., 476
Danowski, T. S., 242, 244, 513
D'Antuono, G., 206
Darby, W. J., 307
Darian Smith, I., 241
Darkshevitch, V. N., 558
Darmady, E. M., 514, 546
Darnis, F., 239, 240
Darte, J. M. M., 241
Das, B. C., 470
Das, N. N., 100
Dasgupta, S. R., 100, 101
Datta, S. M., 477
Daughaday, W. M., 457
Dauzier, L., 474
Davenport, H. W., 32, 179
Davenport, M. W., 135
Davenport, V. D., 32, 135, 179
Davey, D. A., 282
David, J., 381
Davidsen, H. G., 262, 515, 516
Davidson, D. G., 521, 526, 531, 547
Davidson, H. C. C., see Churchill-Davidson, H. C.
Davidson I. C., see Churchill-Davidson, I.
Davidson, M. H., 188
Davies, A. M., 475
Davies, D. D., 139
Davies, G. D. M., see Maengwyn-Davies, G. D.
Davies, H. E. F., 530, 531
Davies, J., 475
Davies, M. K., 188
Davies, R., 29
Davies, R. E., 28, 31, 365
Davies, S. A., 527, 542, 543
Davis, A. H., 126
Davis, F., 165, 274
Davis, G.K., 241, 475
Davis, H., 417, 418, 419, 420, 421, 422, 423, 424, 426, 427, 428, 429, 434
Davis, J.D., 383
Davis, J.O., 239, 246
Davis, M.E., 473, 476
Davis, O.F., 285
Davis, T.R.A., 84, 86
Davis, W.H., 91, 236
Davison, A.N., 131
Davson, H., 13, 28, 63, 71
Dawe, A.R., 84, 91, 373
Dawes, G.S., 155, 166, 381, 383
Dawson, A.B., 472
Dawson, G.D., 490
Dawson, I.M., 491
Dawson, R.M.C., 138
Dawson, W.R., 84, 85
Dawson, W.T., 84
Day, P.L., 307
Deal, C.P., Jr., 266
de Allende, I.L.C., see Allende, I.L.C. de
de Almeida, M.O., see Almeida, M.O. de
Deane, H.W., 453
Deane, N., 522
Deanesly, R., 472
Dearborn, E.H., 535
Deatherage, B.H., 417, 419
Debakey, M.E., 89
de Balsac, R.H., see Balsac, R.H. de
Debley, V., 305
deBurgh Daly, I., see Daly, I. deB.
deBurgh Daly, M., see Daly, I. deB.
de Carli, F., see Carli, F. de
de Comnene, J.S., see Comnene, J.S. de
De Coster, A., 157
Decourt, P., 100
Deering, R.C., 153
de Feurereisen, L., see Feurereisen, L., de
De Geeter, L., 47
DeGroot, C.A., 131
de Groot, J., see Groot, J. de
Deil, J., 135
Deiss, A., 432
Deiss, W.P., 175
de Jongh, S.E., see Jongh, S. E. de
Dejours, P., 154
de Kamer, J.H. van, see Kamer, J.H. van de
Delahaye, D.J., 236
Delaunois, A.L., 274
Del Buono, G., 206
Del Conte, E., 442, 455
de Leeuw, J., see Leeuw, J. de
Delga, J., 89, 101
Delgado, J.M.R., 495, 500
Delgado Febres, E., 233
del Greco, F., see Greco, F. del
Dell, P., 86, 100
Della-Bella, D., 473
Delorme, E.J., 85, 86, 241, 242
Delost, P., 133
del Pozo, E.C., see Pozo, E.C. de
Demeester, G., 268, 378
Demis, C., 26
Dempsey, E.W., 475
Dempsher, J., 407
Dempster, W.J., 525, 545, 546
Denamur, R., 475
De Nicola, P., 207, 210
Denison, M.E., 469
Dennis, J., 503
Dennis, W.H., 16, 179
Denny-Brown, D., 496, 502
Denoël, J.V., see Varetto-Denoël, J.
Denolin, H., 157
Den Ottolander, G.J.H., 211

Denton, A.A., 176
Denton, D.A., 176
De Poli, A., 403, 451
der Lee, S. van, see Lee, S. van
Dernburg, E.A., 500
De Robertis, E., 206, 208
Deroin, J., 134
De Roon, A.C., 51
Derow, M.A., 134
Derrick, J.B., 521
Dervishian, 72
der Werff ten Bosch, J.J. van, see Bosch, J.J. van der Werff ten
Desaive, P., 304
de Sando, T., see Sando, T. de
Deschamps, G., 303
de Schrevel, J., see Schrevel, J. de,
Desclin, L., 472
Descomps, H., 409
Desforges, J.F., 208
De Simone, G., 375
de Sousa, A., see Sousa, A. de
Dessauer, H.C., 128, 193
de Takats, G., see Takats, G. de,
Detrick, L.E., 305
Dettori, A., 208
DeTurk, W.E., 132
Detwiler, S.R., 43, 49
Deuel, H.J., Jr., 305
Deutsch, E., 205, 207, 210, 219, 221, 222
Deutsch, J., 187
Deutsch, L., 375
Devik, F., 301, 308, 309
DeVries, A., 207, 209, 216
DeVries, H., 434
de Wardener, H.D., see Wardener, H.D. de
de Wardener, H.E., see Wardener, H.E. de
Dewhurst, C.J., 476
de Wied, D., see Wied, D. de
DeWitte, J., 378
Dexter, L., 158, 161, 269
Dey, F.L., 458
Deyrup, I.J., 31, 540
Dhyse, F.G., 453
Diamond, I., 378
Dibble, R.F., 524
DiBerardino, M., 47
di Biagio, F., see Biagio, F. di,
Dick, F.W., 209
Dick, J.D., 51
Dickes, R., 375
Dickson, H.M., 185
Diczfalusy, E., 471, 472, 473
Diermier, H.F., 130
Diestel, H.G., 427
Dietmann, K., 101
Digby, P.S.B., 59
di Giorgio, A.M., see Giorgio, A.M.,
Dignam, W. S., 544
Dill, D. B., 87, 92
Dillinger, G. E., Jr., 157
Dimitrijevic, J. N., 86, 96
Dimitroff, J. M., 89
Dineen, J. K., 191
DiPalma, J. R., 90, 370, 373
Dirnberger, P., 210, 214
Dirscherl, W., 473
Di Salvo, R. J., 261
Diserens, H. W., 371
Di Stefano, H. S., 130, 538
Distel, R., 92, 100, 370
Divaris, G. A., 360, 364
Dixon, A. S., 242
Dixon, W. C., 444
Dobin, N. B., 499
Dobson, W. G., 475
Dock, W., 384
Dockerty, M. B., 187
Dodd, M. C., 176
Dodge, H. T., 243, 245
Dodge, H. W., 491, 500
Dodge, H. W., Jr., 176
Doe, R. P., 544
Doherty, D. G., 301, 302, 308
Doigand, A., 183
Doisy, E. A., 473
Doisy, E. A., Jr., 473
Dolan, F. G., 85
Dolaz, E. J., 217
Dolehide, R. A., 217
Domanowsky, K., 469
Dominguez, A. M., 131
Donald, D. E., 381
Donald, K. W., 163, 164, 189, 284, 378
Donato, L., 471
Dong, L., 513
Donner, L., 241
Donnet, V., 85, 100
Donohue, D. M., 231
Donoso, H., 156
Donovan, B. T., 439-66; 409, 446, 458, 469
Dontas, A. S., 267
Dorfman, R. I., 452, 477
Dormer, A. E., 156
Dörner, J., 260, 379
Dornhorst, A. C., 152
Dorpat, T. L., 490
Dorset, V., 264
Dotter, C. T., 287
Doty, R. W., 499
Dougherty, E., 478
Douglas, A. S , 209, 210, 214, 218, 220, 221
Douglas, W. W., 86, 95, 274, 410
Douglass, C. D., 307
Doull, J., 124
Douma, J. H., 285
Dow, P., 285, 374
Dowds, E. G., 266
Downey, V. M., 163, 283
Downing, D. F., 85
Downmann, C. B. B., 407
Drager, G. A., 526
Dragstedt, L. R., 180, 181
Dragstedt, L. R., 2nd, 180
Dray, S., 19
Dreifus, L., 545
Dreiling, D. A., 192
Drenckhahn, F. O., 30, 166, 287
Dresbach, M., 91
Drescher, J., 471
Dresden, D., 359
Drevon, B., 92
Driessens, J., 100
Dripps, R. D , 151
Driscoll, W. T., 46
Droogleever Fortuyn, J., 398
Drorbaugh, J. E., 166
Drosdenko, N. P., 582
Drube, H., 286
Druckman, R., 187
Drumm, A. E., 264
Drummond. J. A., 306
Drury, D. R., 22, 140
Dryer, R. L., 272
Dshavadyan, N. S., 275
Dua, S., 398, 399, 402, 403, 404, 502
Duarte, C. A., 383
Dubecz, S., 91
DuBois, A. B., 158, 165, 192, 269
DuBois, K. P., 124, 134, 304
DuBois, R., 97
Dubrasquet, M., 87, 91, 100, 101
Du Caillar, J., 89
Duchateau, G., 343
Duchême-Marullax, P., 407
Duckert, F., 209, 213, 214
Ducrot, R., 100
Dudel, J., 92
Dudley, A., 218
Dudley, H. C., 179
Duff, F., 257
Duff, J. I., 15
Duff, R. S., 257
Duffy, B. J., Jr., 231, 233, 239, 244
Duke, H. N., 269
Dulbecco, R., 65
Duluc, A. J., 476
Du Mesnil du Buisson, F., 474
Duncan, I. B. R., 180
Dunham, E. T., 22
Dunjic, A., 303, 304, 305, 309, 312, 314
Dunker, E., 23
Dunn, A., 48
Dunn, C. E., 21
Duplan, J. F., 305, 307, 315, 319
Duplessis, H. T., see Tuchmann-Duplessis, H.
Dupond, C., 83
Durante, M., 43, 49
Du Ruisseau, J. P., 140
Dussardier, M., 410
Dustan, H. P., 542

Dutrey, D. E., 277
Dutt, R. H., 469
du Vigneaud, B., see Vigneaud, V. du
Dworkin, S., 86, 97, 98
Dwyer, P., 309
Dyke, H. B. van, 439, 526, 527
Dyrenfurth, I., 246, 476, 541

E

Eakin, R. M., 46
Earl, A. E., 401
East, J., 474
Easton, D. M., 498
Eayrs, J. T., 409, 476, 503
Ebaugh, F. G., 232
Eberhard, T., 452
Ebert, J. D., 44, 385
Ebert, M., 310
Ebert, R. V., 151, 233, 234
Eccles, J. C., 25, 498, 503
Eccles, R. M., 407, 498, 503
Eckel, R. E., 23
Eckstein, J. W., 258
Eckstein, R. W., 381
Edberg, L. J., 135
Eddleman, E. E., 125
Eddleman, E. E., Jr., 375
Edds, M. V., Jr., 47
Eddy, W. H., 307
Edleman, I. S., 185
Edelstein, R., 208
Eden, A., 345
Eden, E., 130
Eder, H. A., 240
Ederstrom, H. E., 84, 502
Edholm, O. G., 85, 98, 256
Edisen, A. E. U., 498
Edler, I., 286
Edlund, T., 306
Edson, J. N., 375
Edstrom, R. F. S., 503
Edwards, C., 15, 407
Edwards, J., 381
Edwards, J. G., 513
Edwards, R. G., 474
Edwards, W. F., 89
Edwards, W. S., 90, 374
Efrati, P., 207
Egan, J. P., 433
Egan, R. W., 381
Egdahl, R. H., 83, 97, 287, 445, 449, 520, 546
Egeli, F. S., 265
Eggers, L. H., 166
Eggleston, M. G., 30, 525
Ehlers, M. H., 477
Ehrner, S. G., 167
Eichhorn, R., 180
Eichna, L. W., 271
Eichner, E., 474
Eik-Nes, K., 444, 453
Eisenberg, S., 231, 233, 238, 239, 240
Eisenmenger, W. J., 240, 245
Eisenstein, B., 284
Eisentraut, M., 83, 84
Eisler, M., 447
Ek, J., 262
Eldjarn, L., 301, 308
Eldredge, D. H., 417, 418, 419, 420, 421, 422, 423, 427, 429, 433
Eldridge, F. L., 166, 381
Eldridge, J. H., 311
Eliasch, H., 262
Eliason, S., 180
Eliasson, R., 475
Eliasson, S., 499
Elion, G. B., 132
Elisberg, E. I., 384
Elithorn, A., 500
Elithorn, I., 499
Elkes, J., 71
Elkin, D. C., 238
Elkinton, J. R., 244, 513, 546
Ellenbogen, L., 183
Ellinger, F., 311
Elliott, H. H., 92, 93
Elliott, K. A. C., 129
Elliott, W. B., 138
Elliott, W. H., 473
Ellis, A., 545
Ellis, D. W., 272, 383
Ellis, F. H., 178
Ellis, K., 305
Ellis, M. E., 308, 312, 313
Ellis, S., 123, 124, 125, 126
Ellman, G. L., 121-50
Elmadjian, F., 444
Elmlinger, P. J., 235
Elosuo, R., 190
Elsner, R. W., 89
Elson, L. A., 303, 314
Elster, K., 184
Elvehjem, C. A., 194
Elvio, F., 86, 96
Elwin, C., 180
Emerson, A. E., 59, 60
Emerson, C. P., 232
Emerson, J., 365
Emery, B. E., 211, 212
Emery, E. W., 530, 531
Emiroglu, F., 24
Emmelin, M. G., 408
Emmelin, N., 278, 407, 409
Emmenegger, H., 211
Endahl, G. L., 478
Endler, P., 157
Endróczi, E., 407, 448, 576, 581
Engel, E., 530, 532, 533, 534
Engel, F. L., 87
Engel, G. L., 188
Engel, S. L., 439, 526
Engelberg, H., 218
Engelhardt, F., 440
Engelman, M., 46
Engle, E. T., 443
Englert, M., 157
Engström, H., 420
Enikeeva, S. L., 373
Ennis, H. L., 50
Enns, T., 29, 270, 522, 524
Epstein, A. W., 501
Epstein, E., 16
Epstein, F. H., 237, 246, 526, 529, 530, 531, 532, 533
Erb, R. E , 477
Erdmann, W. D., 281
Ericsson, U. A., 163
Eriksson, K., 262
Erkelens, A. D., 205
Erlenmeyer, H., 51
Ermakov, N. B., 559
Ernsting, J., 165
Erslev, A. J., 244
Erspamer, V., 362
Ervin, F., 501
Erwin, H. L., 404, 447, 453
Escamilla, R. F., 526
Eskola, O., 380
Eskuche, I., 244
Esselen, W. B., 70
Essex, H. E., 503
Estable, J. J., 67
Estes, J. E., Jr., 271
Eto, M., 93
Eto, T., 470
Etsten, B., 160
Etteldorf, J. N., 521
Euler, C. von, 404, 452, 454
Euler, U. S. von, 272, 273, 360, 439, 444, 519, 520, 543
Evans, B., 529, 531
Evans, D. H. L., 398
Evans, E. I., 241
Evans, H. M., 243, 244
Evans, J., 30
Evans, J. G., 85
Evans, J. R., 186
Evans, S. O., 180
Evarts, E. V., 433
Everett, J. W., 468, 470
Everett, N. B., 232, 234
Ewer, D. W., 337
Ewer, R. F., 350
Ewing, J. H., 162
Ewing, P. L., 160
Eyal-Giladi, H., 42
Eyring, H., 13, 14, 15, 60, 61, 62, 63, 70, 72, 74
Eyzaguirre, C., 491, 498

F

Faarborg-Andersen, K., 499
Fabergé, A. C., 65
Fabian, L. W., 85, 93
Fabre, H., 372, 381
Fabre, J., 541
Fabricus, J., 262, 515, 516
Fadeeva, A. A., 568
Fadiga, E., 126
Fager, C., 400
Fahraeus, T., 71
Fahri, L. E., 157
Fain, P., 503
Fairfield, J., 84

Falbriard, A., 530, 532, 533, 534
Falconer, D. C., 69
Falholt, W., 285, 375
Falk, G., 20
Faller, J., 90, 91
Fanchamps, A., 100
Fanconi, G., 216
Fang, H. S., 233
Fange, R., 362, 363, 368
Fankhauser, G., 48
Fantl, P., 209, 212, 222
Faraghan, W. G., 315, 317, 318, 319
Farah, A., 123, 130, 131, 370, 379, 538
Farah, H. E., 122, 123
Farber, D. A., 569
Farhi, L. E., 269
Farinella-Ferruzza, N., 51
Farquhar, M. G., 440
Farr, A. F., 166
Farr, L. E., 240, 245, 371
Farrar, J. T., 192
Farrell, G. L., 451, 541, 542
Fatt, P., 25, 498, 503
Faucett, R. L., 501
Faulk, M E., 494
Faure, J., 284
Fauré-Fremiet, F., 72, 74
Fautrez, J., 47
Fautrez-Firlefyn, 47
Favre, R., 101
Fawaz, E. N., 131
Fawaz, G., 124, 131, 378
Fawcett, D. W., 89
Fay, T., 86, 93
Fayot, G., 101
Fazekas, J. F., 94
Fearnley, G. R., 217
Feaster, J. P., 475
Featherstone, R. M., 126, 132
Febres, E. D., see Delgado Febres, E.
Fedeli, S., 402
Feder, W., 286
Federschmidt, K., 92
Fedor, E. J., 96, 189
Fedorov, V. K., 570, 572, 581
Fedotov, J. P., 571
Feichtmeir, T. V., 542
Feigelson, E., 365
Feigenbaum, L. Z., 189
Feinmann, L., 166
Feinschmidt, O., 91, 93
Feinstein, R. N., 305, 307
Feissly, R., 209
Fejfar, Z., 260
Fekete, A., 519, 520, 545
Felberbaum, I. M., 576
Feldman, J., 97
Feldman, M., 43, 44, 46
Fell, C , 217, 218, 219
Feller, D. D., 231, 233, 234, 271, 285, 375
Feller, K., 100
Fellinger, K., 175, 206
Fellinger, K., 175, 206
Feltman, R., 475
Felts, J., 182
Felts, J. M., 189
Feltynowski, F , 206
Fencl, V., 520
Fenichel, R. L., 208
Fenn, W. O., 151, 163, 166, 309, 343
Ferdmann, D., 91, 93
Feremutsch, K., 401
Fergus, E. B., 242
Ferguson, D. J., 476
Ferguson, F. C , 125
Ferguson, J. H., 205, 210, 310, 311
Ferguson, R. W , 261, 264
Ferguson, T. B., 237, 377
Fernald, G. D., 383
Fernald, J. D., 239
Fernandes, J., 185
Fernandez, C., 420, 421, 423, 425, 427, 428, 429
Ferrante, W. R., 278
Ferrari, E , 94
Ferrer, M. I., 377
Ferres, H. M., 256, 275
Ferri, L., 303, 305
Ferris, E. B., 261
Ferriss, G. S., 500
Ferruzza, N. F., see Farinella-Ferruzza, N.
Fertig, J W., 305
Fetzer, S., 471
Feurereisen, L., de, 183
Fevold, H. L., 469
Feyel-Cabanes, T., 473
Fiala, S., 221
Fick, K. H., 235
Ficq, A., 43, 46
Fiehrer, A., 213, 218, 219
Field, H., 184
Field, J., 61
Field, J., 2nd, 60, 66, 70, 92
Fieldman, E. J., 383
Fields, M., 240, 245
Fieschi, A., 206
Fievez, C., 303
Figen, J. F., 130
Figueroa, W. G., 216
Filkula, J., 87
Finch, C. A., 187, 231, 243, 245
Finch, S. C., 238
Fine, D , 246
Fine, J., 282
Finean, J. B., 71
Finerty, J. C., 309, 313, 314, 318, 442
Fink, B. R., 156
Fink, L. D , 409
Finkelman, I., 499
Finkelstein, M., 127
Finkle, J. R., 499
Finlayson, J. S., 524
Finley, C. B., 61
Finnegan, C. V., 49
Finney. W. H., 86, 97, 98
Firestone, J. E , 93
Firket, J., 316
Firlefyn, N. F., see Fautrez-Firlefyn, N.
Firsov, L. A., 583
Fischer, C. S., 122
Fischer, H., 124
Fischer, M. A., 305
Fischer, P., 303, 304, 306, 307, 308, 362
Fischgold, H., 497
Fisher, B., 96, 189
Fisher, E. R., 96
Fisher, O. D., 207
Fisher, R. B., 184
Fishler, M. C , 312, 313, 315, 316, 317
Fishman, A. P., 154, 533
Fishman, I. Y., 491
Fister, G. M., 523, 536
Fitch, F. W., 304
Fitz, R. H , 538
Fitzgerald, L. R., 84
Fitzgerald, M. A., 218
FitzGerald, M. G., 529, 542
Fitzhugh, F. W., 520, 547
Flagg, W., 60, 61, 65, 66, 67
Flagler, F. A., 74
Flamboe, G. E., 124
Flamm, G. H., 375
Flanders, P. H., see Howard-Flanders, P.
Flanigan, S., 399, 401, 501, 502
Flath, R., 286
Flax, L. J., 526
Fleckenstein, A., 126, 365
Fleischer, E., 268
Fleming, D. G., 409
Fleming, E. M., 71, 72
Fleming, R., 91
Flerchinger, F. H., 477
Fletcher, H., 427
Flink, E. B., 544
Flint, J. S., 309
Florens, A., 157
Florentin, A. A., 444
Florey, E(lizabeth), 362
Florey, E(rnst), 362, 407, 503
Florey, H., 182
Florey, H W., 182, 183
Florio, M. S., 67
Florkin, M., 342, 343
Flottorp, G., 434
Floyd, W. F., 499
Flückiger, E , 15, 96
Flückiger, P., 213
Flury, E., 471
Flux, D. S., 476
Flynn, J. E., 220, 221
Flynn, J. P., 399, 401, 501, 502
Foerster, H. von, 502
Fogelman, M. J., 208, 241
Földi, M., 166, 547

Folk, G. E., 92
Folkes, J. P., 29
Folkow, B., 155, 156, 257, 259, 275, 276, 277
Folley, S. J., 468, 470, 476
Foltz, E. L., 493
Fonio, A., 207
Fonnescu, A , 28
Fontaine, M., 85, 87, 96, 347, 348
Fontaine, T. P., see Passouant-Fontaine, T.
Forbes, A. P., 457
Forbes, W. H., 87, 92
Ford, A. B., 238
Ford, C. E., 319, 320
Ford, H , 181
Ford, R. V., 519, 547
Forel, M. M , 214
Foreman, C. W , 92
Foreman, N., 183
Forker, L., 245
Forni, R. B., 100
Forro, F., Jr., 299, 300
Forsham, P. H., 457
Forssander, C. A., 166
Forster, E , 100, 102
Forster, F. M., 500
Forster, R. E., 156
Forster, R. P., 31, 100, 520, 536
Fortier, C., 44, 446, 447, 449, 454
Fortuyn, J. D., see Droogleever Fortuyn, J.
Foster, C. A., 256
Foster, G. L., 86
Foulkes, E. C., 26
Foulks, J., 544
Fourman, P , 529
Fournel, J., 100
Fornie, G., 384
Fournier, J. E., 433
Fowler, C., 331
Fowler, N. O., 281, 283, 375
Fowler, W. A., 156
Fowler, W. S., 157, 159
Fowweather, F. S., 523
Fox, A., 261
Fox, A. C., 239
Fox, C. L., 242
Fox, I. J., 285, 374
Fox, M., 300, 301, 303, 304, 305, 306, 307
Fox, R. H., 256
Foxon, G. E. H., 385
Foye, L. V., Jr., 542
Fraction, G. F., 96
Frahm, H., 471
France, E. S., 218
Franch, R. H., 283
Francis, C. M., 491
Francis, F. E., 473
Franco, N., 101, 490
Frank, C. W., 237
Frank, E., 371
Frank, E. D., 282
Frank, E. J., 308
Frank, H., 233
Frank, H. A., 241, 282
Frank, H. D., 188
Frank, K., 498
Franke, E. K., 433
Franke, H., 259
Frankland, M., 194, 195
Franklin, K. J., 476
Franklin, M. H., 189
Franksson, C., 444
Fraps, R. M., 469
Fraser, I., 187
Fraser, R., 133
Fraser, R. W., 457
Frawley, J. P., 191
Frazer, J. F. D., 475
Frederick, W. H., 375
Fredrickson, D. S., 404, 446, 448, 455, 457, 468
Freed, S. C., 272, 372
Freedman, D. A., 50
Freedman, M. E., 268, 283, 378
Freeman, J., 307
Freeman, L., 218
Freeman, O. W., 520, 547
Frreman, S., 536
Fregley, M. J., 284
Fregly, M. J., 89, 97, 167
Freier, E. F., 365
Freinkel, N., 233, 238
Freire, J. R. C., see Correa Freire, J. R.,
Freireich, E. J., 238
Freis, E. D., 160, 238, 239, 268, 281, 377
Fremiet, F. F., see Fauré-Fremiet, F.
Fremont-Smith, K., 245
French, E. B., 261
French, G. M., 500
French, J. D., 399, 493, 499
French, L. A., 411
French, R. G., 402
French, R. M., 231, 238
Fretter, V., 333
Freund, H., 86
Frey-Wyssling, A , 72
Frick, P. G., 212, 216
Fridhandler, L., 187, 475
Fried, P. H., 475
Fried, W., 244
Friedell, H. L., 301
Frieden, E., 135
Frieden, E. H., 474
Friedenwald, J. S., 141
Friedgood, C. E., 86
Friedman, B., 285
Friedman, C. L., 519, 527
Friedman, I. A., 217
Friedman, I. H., 281
Friedman, M., 186, 189, 192
Friedman, S. M., 519, 527
Friese, G., 383
Friesen, S. R., 184
Frigerio, N. A., 132
Frischauf, H., 222
Froeb, H. F., 270
Frolkis, V V., 370
Froman, D. K., 59, 70
Fronius, E. K., see Kerpel-Fronius
Frost, L. L., 492, 496
Frowein, R. A., 101
Fry, E. G., 449
Fry, F. J., 504
Fry, W. J., 504
Fryer, J. H., 193
Fryers, G. R., 235, 243
Fuchs, F., 237
Fuhrman, F. A., 60, 64, 66, 70, 92, 350
Fuhrman, G. J., 60, 70, 92
Fujii, T., 47
Fujimori, H., 365
Fukarek, V., 187
Fukuda, M., 449, 451, 468, 469
Fukushima, K., 70
Fulford, B. D., 403, 447, 448, 450
Fuller, G. R., 529, 530, 531, 532, 533
Fuller, J. L., 402
Funel, P., 213, 218, 219
Funes, J. R. C., see Cordero Funes, J. R.
Fuortes, M. G. F., 498
Furth, J., 299, 300, 306, 439
Furuhjelm, M., 474
Fuse, S., 400
Fyke, F. E., Jr., 177

G

Gacek, R. R., 428
Gaensler, E. A., 165, 269
Gaertner, R., 545
Gaertner, R. A., 377
Gagliani, J., 449
Gagnon, J. A., 522
Gagnon, J. O., 185
Gaillard, R., 86
Gaitonde, M. K., 503
Galambos, R., 399, 401, 417, 428, 430, 431, 500
Galdston, M., 154
Gale, E. F., 29
Galinier, F., 515
Galloway, T. M., 348
Galvan, A. O., see Ortiz-Galvan, A.
Galvin, R. D., 447
Gambarian, L. C., 571
Gambescia, J. M., 190
Gamble, H. J., 398, 501
Gammill, J. F., 239, 383
Gangadharam, P. R. J., 131
Gangloff, H., 399
Ganguli, N. C., 215
Ganis, F. M., 133
Ganong, W. F., 32, 97, 371, 404, 445, 448, 449, 468
Ganschow, R. E., 474
Gänshirt, H., 94, 100, 127

Garb, S., 365, 369, 370, 379
Garby, L., 27, 29, 522
Garcia, J. F., 243, 244
Gardier, R. W., 538
Gardner, A., 494
Gardner, E., 405, 491, 494
Gardner, E. A., 123
Gardner, F. H., 184
Gardner, W. J., 175
Garner, E. S., 219
Garner, J. L., 308
Garoutte, B., 503
Garrett, J., 383
Garrod, O., 527, 542, 543
Garrong, W. F., 180
Garry, R. C., 188, 410
Gaskell, P., 256, 258
Gasser, H. S., 397, 491
Gassner, F. X., 477
Gasster, M., 183
Gaston, E. O., 310, 311, 314
Gates, A. H., 475
Gatt, S , 132
Gatti, G. L., 281
Gauchery, O., 140
Gauer, O. H., 158, 231, 243, 245, 246, 268, 275, 281, 283, 286, 520
Gaughran, E. R. L., 60
Gaunt, R., 401, 439, 449, 541
Gaupp, V., 441, 446, 468
Gause, G. F., 353
Gawron, O., 135
Gebhard, J. W., 433
Geddes, L. A., 91
Gee, J. B , 153
Gehenio, P. M , 65, 66
Gehmacher, K., 216
Gehrsitz, L. B., 93
Geiger, A , 503
Geiger, E., 94, 194
Geiling, E. M. K., 124, 128, 384
Gele, P., 210
Gelfant, S., 472
Gelineo, A., 84
Gelineo, S., 84, 87, 89
Gell, C. F , 93
Gellhorn, E., 73, 94, 95, 97, 276, 400
Gemmill, C. L., 135
Gemzell, C. A , 236, 237, 243, 444
Genaud, P. E., 314
Genesi, M., 470
Genest, L. C , 98, 101
Genovese, E., 473
Gensini, G., 158
Georgatsos, J. G., 208
George, R., 448
Georges, G., 87, 97, 101, 102
Gerard, R. W., 20, 94, 132, 276, 405, 489, 496, 503
Gerebtzoff, M. A., 303, 306, 307, 308
Geren, B. B., 19
German, W. J., 281
Gernandt, B. E., 433, 493, 499
Gernhardt, B. E., 399
Gerova, M., 260, 520
Gerritsen, T., 237
Gerschman, R., 163, 309
Gersh, I., 526
Gershberg, H., 93, 96
Gershouni, G. V., 561
Gerst, P. H., 280
Gerstber, R , 67
Gertler, M. M., 369
Geyer, G., 271, 400
Gherardi, G., 60, 62, 74
Ghiggino, C. W., 265
Ghiretti, F., 362
Giaja, G., 86
Giaja, J., 85, 86, 87, 88, 89, 90, 92, 93, 96, 98
Giaja, L. M., see Markovic-Giaja, L.
Giardina, G., 44
Gibertoni, G., 134
Giblett, E. R., 231
Gibree, N. R., 444
Giebisch, G., 528, 533, 537, 543
Gierke, E. von, 433
Gierlach, Z. S , 453
Giese, A. C., 64, 73, 74
Gifford, R W., Jr., 271
Gigee, W., 367
Gilbert, C., 471
Gilbert, D. L., 103, 309
Gilbert, J. P., 183
Gilbert, M., 367
Gilbert, R., 94
Gilbert, R. P., 239, 261
Gilder, H., 239, 240
Gilford, S. R., 285
Gillespie, J. S., 188, 410
Gilliland, I. C., 456
Gillman, J., 471
Gilman, M., 449
Gilse, H. A. van, 471
Gilson, J. C., 156
Giltaire-Ralyte, L., 166
Gingliner, A., 84
Ginsburg, J., 216, 257
Ginski, J. M., 93
Giono, H., 91
Giorgio, A. M. di, 95
Giotti, A., 123, 125
Giraud, G., 372
Girdwood, R. H., 183
Giroud, C. P., 246, 541
Gisselsson, L., 499
Githler, F. J., 432
Gitlin, D , 240, 245
Gittinger, W. C., 370
Giulio, L , 376
Glaesser, H., 368
Glaid, A. J., 135
Glaser, G. H., 499, 500, 504
Glass, G. B. J., 183
Glassman, M., 124
Glassner, H. G., 380
Glasstone, S., 61, 62, 63
Glaviano, V. V., 154, 537, 593
Glees, P., 504
Glick, D., 320
Glickman, N., 235
Glilkman, 131
Gloor, P., 400
Glover, T. D., 478
Glueck, H. I., 210, 216
Goas, M., 73
Godden, J. O., 261
Goding, R. D., 176
Goetsch, C., 236, 237
Goetz, A., 66
Goetz, S. S., 66
Goffrini, P., 101
Gökhan, N., 152
Golbey, M., 91
Gold, G. L., 14, 22
Gold, H., 370
Goldacre, R. J., 331
Goldberg, M., 239
Goldbloom, A. A., 183
Goldensohn, E. S., 152, 497
Goldfarb, M., 369
Goldfien, A., 449, 453
Goldman, E , 503
Goldman, R., 240, 245, 271, 544
Goldner, M. G., 130
Goldsmith, J. R., 137
Goldstein, A. C., 404
Goldstein, L., 405, 535
Goldstein, M. S., 22, 132
Goldstein, R., 210, 420, 423, 426, 427, 428, 429
Goldsworthy, P. D., 245
Goldwasser, E., 244, 311, 317
Gollan, F., 85, 86, 88, 91, 167, 373
Gollub, S., 208
Goltz, F., 86
Golub, J. R., 246, 520
Golub, L. M., 500
Gomez, A., 68
Gompertz, M. L., 189
Gonlubol, F., 125
Gonnard, P., 131, 408
Gonzales, F , 68
Goodale, W. T., 383
Goodeve, C. F., 64
Goodhill, V., 433
Goodman, H., 545
Goodman, H. C , 233
Goodman, J. R., 23, 513
Goodman, L. S., 449
Goodman, M., 474
Goodman, R. D , 178
Goodner, C. J., 184
Goodsell, M. G., 544
Goodwell, H., 70
Goodyer, A. V. N., 246
Goosselnikov, V. I., 580
Göral C., 410
Gorbman, A., 132, 439
Gordh, T., 153, 164
Gordon, A. J., 281, 371

Gordon, A S , 244
Gordon, E. E , 133
Gordon, H. H., 192
Gordon, J. G., 193
Gordon, R. A., 87, 100
Gorini, L., 45
Gorlin, R., 161
Gormsen, H., 514
Gornall, A. G., 475
Goss, H., 137
Gosset, J., 100
Gossweiler, N., 20
Goth, A., 401
Goto, T., 497
Gottfried, S. P., 443
Gottschalk, C. W., 515, 516, 525
Gottstein, U., 92, 259
Gould, B. S., 60, 132
Gould, R., 162
Gould, R. P., 91, 154
Gouliaev, P. I., 566
Goumenuk, I. G., 563
Gourley, D. R., 23
Gouzon, B., 100
Gowdey, C. W., 377
Gowen, J. W., 477
Gozzano, M., 399
Grace, F. T., 380
Grace, J. B., 285
Grace, J. T., 85, 86, 91, 373
Grace, W. J., 444
Graf, K., 261
Graf, W., 265, 490
Grafe, E., 86
Graff, M. M., 453
Graff, S., 46
Grafflin, A. L., 346
Grafstein, B., 500
Graham, G., 131
Graham, G. R., 90
Graham, J. B., 211
Gramiak, R., 263
Granata, L., 274
Grandell, F., 384
Grandell, F. M., 375
Granit, R., 489, 491, 496, 497
Grant, A., 183
Grant, F. C., 458
Grant, K. B., see Brown-Grant, K.
Grant, N. H., 191
Grant, R., 86
Grant, W. C., 231, 243, 244
Grastyán, E., 406, 565, 576
Gray, D. H., 73
Gray, F. C., 157
Gray, F. D., Jr., 157
Gray, G. W., 410
Gray, J. A., 25
Gray, J. S., 152
Gray, L. H., 299, 300, 301, 308
Gray, N. N., 86
Gray, S. J., 32, 180, 182, 231, 233, 439
Gray, S. L., 301
Greathouse, R., 533
Grebenkina, M. A., 576
Greco, F. del, 525, 526
Green, G. E., 176
Green, H. D., 266
Green, I., 515, 516
Green, J. D., 399, 400, 441, 468, 469, 489, 501, 526
Green, J. E., 236
Green, J. H., 152, 153, 274, 275, 409
Green, J. P., 140
Green, J. W , 23
Green, L. F., 133
Green, M. N., 136
Green, S. H., 471
Greenberg, L. J., 128
Greene, H., 372
Greene, H. S. N., 44
Greene, L. C , 279
Greene, R. W., 217
Greenfield, A. D. M., 257, 258
Greenfield, P., 45, 503
Greenman, L., 242
Greenstein, J., 194
Greenwald, J., 188
Greenwalt, T. J., 220
Greenwood, W. F., 87, 90, 91, 100
Greer, M. A., 177, 403, 404, 448, 453, 454, 455
Greganti, F. P., 281
Gregersen, M. I., 232, 233, 234
Gregg, A., 3
Gregg, D. E., 90, 237, 263, 285, 366, 374, 377, 378
Gregg, J. H., 50
Gregg, J. R., 44
Gregoire, C., 207
Gregoretti, L., 401, 440
Gregory, R. L., 491, 502
Greif, R. L., 240, 530, 537, 538
Greiner, T , 122
Greipel, M., 194, 195
Greisheimer, E. M., 272, 383
Grenan, M. M., 311
Grenberg, J., 179
Grenell, R. G., 127, 503
Greville, G. D., 136
Grey Walter, W., 495
Gribetz, D., 522, 536
Grieg, A., 31
Grieg, M. E., 140
Griesbach, W. E., 441, 442
Griesemer, E. C., 131
Grieser, K. C., 470
Griffin, G. E., 532, 533, 535, 537
Griffin, J., 239
Griffin, R. W., 519, 547
Griffith, A., 187
Griffith, C. A., 182
Griffith, H. W., 231, 233, 239, 244
Griffith, W. P., 93
Griggs, N., 233
Grignon, G., 402
Grim, E., 19, 184, 270
Grindlay, J. H., 185, 190
Grinspoon, L., 210
Grisolia, S., 137
Grison, P., 69
Grobstein, C., 43, 545
Grodins, F. S., 152, 154
Grollman, A., 244
Groom, A. C., 285
Groot, J. de, 301, 448
Gros, C. M., 304, 307, 308
Gross, A., 277
Gross, D., 372
Gross, N. B., 430, 431
Grosse-Brockhoff, F., 91
Grossman, C., 494
Grossman, F. M., 433
Grossman, H. J., 166
Grossman, J., 525, 526, 537
Grossman, M., 182
Grossman, M. I., 191
Grossman, R. G., 402
Groves, P. W., 43
Grubbs, R. C., 503
Gruhzit, C. C., 122, 123, 379
Grumbach, N. M., 443
Grundfest, H., 17, 20, 492
Grupp, G., 286
Gruskay, F. L , 187
Gualtierotti, T., 493
Guareschi, A., 94, 101
Guelfi, J., 96, 101
Guerin, J., 379
Guest, M. M., 217
Guiguet, C., 476
Guild, W. R., 545, 546
Guillemin, R., 403, 404, 447, 450
Guillemot, R., 383
Guillery, R. W., 398
Guillot, N. G., 74
Guinard, A., 217, 218
Guittard, R., 101
Gullino, P., 194
Gullixson, K. S., 547
Gunberg, D L., 443
Gunn, D. I., 59
Günther, B., 268, 284
Gunton, R. W., 231, 233, 238, 239, 272
Gurevitch, J., 207, 208
Gurevitch, V., 210
Gustafson, A., 286
Gustafson, T., 46
Guth, L., 410
Guth, P. H., 191
Guttentag, O., 233, 234
Guttman, L., 275
Guyon, M., 364
Guyton, A. C., 377
Gwathmey, O., 85
Gyermek, L., 86
György, L., 277
Gyser, T. H., 155
Gyster, M. J., 129

H

Haag, V., 478
Haas, B., 100
Habermeyer, J. G., 310, 319, 320
Habif, D. V , 216
Hackel, D. B., 383
Hackel, D. V., 263
Hackney, A. L., 50
Haddow, A., 132
Haddy, F. J., 261, 519
Hadek, R., 472
Haeger, K., 86
Hafez, E. S. E., 475
Haft, D. E., 126
Hagbarth, K. E., 491
Hagberg, K., 11
Hagedorn, M. B., 166
Hagen, E , 402
Hagen, P. S., 73, 212
Hagen, U., 301, 308
Hagiwara, F., 448
Hagiwara, S., 359, 491
Hagopian, M., 475
Hagstam, K.-E., 157
Hagström, B , 47
Hajdu, A., 519
Hajdu, S., 68, 69
Hajdukovic, S., 65, 89, 96, 308
Hald, P. M., 240, 245
Hale, J. F., 286
Hale, W. M., 317
Haley, T. J., 305, 306, 307
Hall, C. E., 371
Hall, E. K., 369
Hall, H. B., 374
Hall, K., 474
Hall, M., 502
Hall, O., 371
Hall, P. W., 3rd, 543
Hall, R. M , 188
Hallaway, B. E., 365
Hallberg, L., 241
Halliday, R., 475
Hallman, L. F., 453
Hallpike, C S., 433
Halmi, N. S , 404, 442, 454, 455, 468
Halonen, P. I., 380
Halperin, M. H., 246, 262
Halpern, B. V., 100
Halpern, M. H., 536
Halstead, J. A., 183
Halstead, W. C , 433, 501
Ham, G. C., 455
Ham, T. H., 71, 72
Hamburger, C , 449
Hamburger, V., 49
Hamerton, J. L , 319, 320
Hamilton, J. B., 91, 477
Hamilton, L., 285
Hamilton, L. H., 232
Hamilton, R. S., 91
Hamilton, W. F., 374
Hamlin, H., 500
Hamlyn, L. H., 398, 501
Hammarsten, J. F., 233
Hämmerli, A., 175
Hammond, W. S., 49
Hamolsky, M. W., 453
Hampton, M. N., 307
Hanbery, J., 493
Handel, M., 283
Handforth, C. P., 166
Handler, P., 519
Handley, C. A., 130
Hane, S., 443, 444
Hanke, M. M., 181
Hankinson, J., 496
Hanley, T., 532, 533
Hanna, C. H., 271
Hanno, M. G. W., 133
Hanon, F., 472
Hans, M. J., 475
Hansard, S. L., 475
Hansel, W., 468
Hansen, A. T., see Tybjaerg Hansen, A.
Hansen, C., 141
Hansen, D. B., 91
Hansen, R. A., 309
Hanström, B., 441
Hanusek, G., 374, 515, 522
Hara, M., 85, 93
Harbough, F. G., 503
Hardaway, R. M., 188, 208
Hardiman, C. W., 491
Hardin, B., 537
Hardin, J. O., 129
Hardisty, M. W., 348
Hardisty, R. M., 220
Hardung, V., 278, 279
Hardy, E. G., 89
Hardy, J. D., 70
Hare, K., 543
Hare, R. S., 543
Harkins, H. N., 182
Harlow, H., 500
Harper, A. E., 194
Harpman, J. A., 490
Harrevald, A. van, 25, 500
Harrington, W. J., 208
Harris, A. S., 370
Harris, D. L., 28
Harris, E. J., 13-40; 13, 14, 15, 18, 20, 22, 25, 31
Harris, G. W., 439-66; 400, 403, 439, 444, 446, 447, 448, 449, 451, 452, 453, 454, 455, 468, 469, 502, 504, 526
Harris, J., 136
Harris, J. D., 433
Harris, J. E., 71, 93
Harris, J. H., 192
Harris, J S., 521
Harris, P., 379, 383
Harris, R. J. C., 66
Harrison, D. D., 130
Harrison, F., 401
Harrison, G. F., 188
Harrison, H. C., 536
Harrison, H. E., 536
Harrison, R. C., 87, 100
Harrison, W. K., Jr., 286, 375
Harriss, E. B., 314
Harrold, C. C., 454
Harsing, L., 99
Hart, J. S., 86, 89
Hartleb, O., 166
Hartcroft, P. M., 543
Hartroft, W. S., 543
Hartwell, S. W., 180
Haverback, B. J., 181
Harvey, E. N., 74
Harvey, J. H. P., 133
Harvey, R. B., 155, 452
Harvey, R. M., 377
Harvey, S. C., 21, 124, 364, 384
Hasbrouck, E. E., 545
Hashimoto, K., 140, 369
Hassan, M. I., 265
Hassan, M. J., 189
Hasselbach, W., 124
Hastings, A. B., 14, 93
Hastings, B., 92
Hata, D., 160, 262, 384
Hataway, G. D., 283
Hatcher, J. D., 236, 246, 262, 285
Hatcher, J. D., 377
Haterius, H. O., 90
Hattingh, I., 337
Haugen, F. P., 492
Haupt, H., 85
Haurowitz, F., 75
Hauser, F., 222
Hausler, H. F., 101
Hauss, W. H., 276
Hawa, E. S., 124
Hawkins, L. W., 365
Hayashi, Y., 41, 42
Haydar, N. A., 439
Hayes, E. W. Jr., 167
Hayes, F. R., 60, 343
Hayes, R. A., 209
Haymaker, W., 92, 163, 283, 406
Haynes, F. W., 158, 161, 269
Hays, D. R., 246, 520, 524
Hayward, H. R., 29
Haywood, C. A., 363
Hazard, R., 372, 408
Heagy, F. C., 86
Hearn, W. R., 403, 450
Hearon, J. Z., 136
Heath, C., 283
Heath, H. D., 74
Heath, R. G., 399, 400, 494
Heatley, N. G., 182
Hebb, D. O., 444
Hecaen, A., 500
Hecaen, H., 499
Hecht, E., 208
Hecht, H., 276
Hecht, H. H., 92
Hechter, O., 132, 282
Heckel, N. J., 478

Hecker, R., 189, 266
Hedlund, S., 233, 238, 239
Heemstra, H., 151
Hegglin, R., 285
Heglin, J , 306
Hegnauer, A. H., 90, 93, 235, 236, 343, 373
Heidelmann, G., 282
Heidenreich, O., 263
Heilbrun, A. B., 499
Heilbrunn, L. V., 47, 48, 353
Heim, F., 100
Heim, G., 473
Heinbecker, P., 452
Heinecker, R., 284
Heinemann, H. O., 526, 533
Heinkel, K., 184
Heinrichs, H. D., 471
Heintzen, P., 92
Heinz, E., 28, 32
Heinzen, B., 271
Heise, G. A., 431
Hejl, Z., 520
Hele, P., 366
Helfer, R. G., 338
Hellbaum, A A., 472
Heller, B. I., 233
Heller, H., 349, 350
Hellman, K., 385
Helmendach, R. H., 86
Helmholz, H. F., Jr., 157, 159
Helrich, M., 123, 242, 272, 376, 383
Helwig, H. L., 242
Hemingway, A., 157, 404, 496, 502
Hemmer, M. L., 370, 372
Hemmings, W. A., 44
Hemplemann, L. H., 89
Hempling, H. G., 24, 28
Hendershot, L. C., 127, 410
Henderson, C. B., 286
Hendricks, C. H., 375, 383, 520, 547
Henning, N., 184
Hennington, R., 208
Henrie, J.R., 503
Henry, J., 231, 243, 245
Henry, J.P., 158, 245, 246, 268, 275, 281, 283, 520
Henry, R., 449
Henry, W., 22
Henschel, A., 325, 236, 245
Hensel, H., 59, 70, 73, 74, 75, 85, 131, 255, 259
Hepper, N.G., 381
Herbertson, M.A., 46
Herbst, F.S.M., 271
Hercus, V.M., 21, 385
Herlant, M., 83, 470
Hermann, H., 45
Hermans, N., 126
Hernandez, T., 533, 535
Hernandez-Peon, R., 500
Herndon, R.F., 371
Herold, G., 216
Heroux, O., 86
Herr, E.B., 302, 308
Herranen, A., 133, 473
Herring, P.T., 93
Herrmann, H., 46, 473
Herrmann, M., 471
Herrmann, R.G., 124
Hershberger, R.L., 519, 547
Herter, K., 69
Hertig, A.T., 475, 478
Hertz, C.W., 268
Hertz, R., 453, 473
Herve, A., 65, 89, 299, 300, 304, 305, 306, 307
Herz, G., 377
Hess, A., 397, 490, 502
Hetenyi, E., 257
Hetzel, B.S., 444
Hetzel, P.S., 161
Heuts, M.J., 336, 337, 338, 342, 346, 347, 353
Hevesy, G., 232
Hey, W., 281
Heyer, H.E., 381
Heyman, A., 264
Heyman, F., 281
Heymans, C., 274
Heymans, J.F., 86
Hiatt, C.W., 233
Hickam, J.B., 283
Hicks, N.D., 220
Hiebel, G., 86, 88, 87, 90, 91, 100, 102
Hiestand, W.A., 87, 89
Higashi, K., 472
Higashida, S., 407
Higgons, R.A., 194
Hightower, N.C., Jr., 178
Hilali, S., 431
Hild, R., 376, 377
Hild, W., 350, 441
Hildes, J.A., 384
Hilding, A.C., 433
Hilfinger, M.F., Sr., 310, 311
Hill, A.V., 21
Hill, J.M., 210
Hill, R.M., 85
Hill, S.R., 444, 457
Hill, T.L., 124
Hillarp, M.-A., 458
Hille, H., 259
Hillebrecht, J., 471
Hilton, J.G., 154, 246, 274, 376, 520, 524, 537, 539
Hilton, S.M., 175, 276
Himelson, A., 281
Himmelstein, A., 281, 371
Himwich, H.E., 94, 401, 493, 503
Hind, J.E., 429, 431, 432
Hine, C.H., 127
Hines, E.A., 261
Hingerty, D., 26
Hinton, H.E., 74
Hinton, J.W., 410
Hirsch, B.B., 310, 315, 317, 318, 319
Hirsch, H., 94, 101
Hirschowitz, V.I., 180
Hirsh, H.M., 302, 308
Hirsh, I.F., 433
Hirsjarvi, E., 244
Hirvonen, L., 91, 92
Hisaw, F.L., 473
Hiscock, I.D., 343
Hitchcock, D., 19
Hitchcock, F.A., 283
Hitchings, G.H., 132
Hjelmquist, U., 490
Hjort, P., 220, 221
Hlad, C.J., Jr., 232
Hoagland, H., 444
Hobson, A.D., 344, 345
Hoch, F.L., 133
Hochstetler, S.K., 315, 317, 318, 319
Hochwald, I.B., 64
Hock, R.I., 60, 65, 66, 67
Hockerts, T., 380
Hodapp, E.I., 66, 70
Hodges, C.V., 514
Hodges, J.L., Jr., 233, 234
Hodgkin, A.L., 13, 17, 18, 20, 25, 26, 61, 72, 336, 343, 349
Hodgkins, E.J., 71
Hodgkinson, M.M., 369
Hodgson, E.S., 410
Hodgson, G., 244
Hodler, J., 533
Hoeltzenbein, J., 246
Hoen, N.L., 67
Hoene, R., 306
Hofer, R., 175
Hoff, H.E., 91, 96, 101, 504
Hoffheinz, H.J., 268
Hoffmann, F., 476
Hoffmann, H., 490
Höfler, W., 85
Hofman, D., 305
Hogben, C.A.M., 18
Hogness, J.R., 453
Höhne, G., 304
Hoi, N.P.B., see Buu-Hoi, N.P.
Hoitink, A.W.J.H., 87, 96
Hokin, L.E., 135
Hokin, M.R., 135
Holaday, D.A., 94, 166
Holcomb, A.L., 433
Holden, E., 401
Holdgate, M.W., 339
Holette, C., 191
Hollaender, A., 299, 300, 309
Holland, R.C., 443
Holland, W.C., 21, 530
Hollander, F., 193
Hollander, P.B., 373
Hollander, W., 177, 246, 262, 527
Holley, H.L., 513
Holliday, M., 527
Holling, H.E., 165
Hollister, L.E., 190
Holman, C.B., 500
Holman, E., 238

Holmberg, J., 305, 306
Holmberg, N.G., 475
Holmdahl, M.H., 165
Holmes, B.E., 299
Holmes, J.H., 86, 90, 117, 232, 410
Holmes, O., 490
Holmes, R., 531
Holmes, T.H., 490
Holmes, T.M., 89
Holmgren, A., 234
Holmgren, B., 404, 454, 489, 496
Holtfreter, J., 42, 43
Holtkamp, W., 91
Holton, F.A., 366
Holton, P., 277
Holtz, P., 368
Holtzer, H., 43, 51
Holtzer, S., 51
Holzach, O.B., see Brenner-Holzach, O.
Homann, W., 89
Hon, E.H., 475, 476
Hong, S.K., 99, 520, 526, 547
Hong, S.S., 190, 191
Hoobler, S.W., 547
Hood, J.D., 433
Hood, M., 529, 531, 538
Hoogstra, M.J., 470, 471
Hook, W.E., 91
Hoorweg, P.G., 211
Hope, A., 237, 271
Hopkins, D.L., 331
Hopper, J., Jr., 231-254; 231, 232, 233, 234, 238, 240, 244
Hopps, J.A., 86, 92, 93
Hori, R., 42
Horiuchi, K., 407
Horn, E.H., 477
Horn, R.G., 186
Horn, R.H., 88, 154
Hornsby, S., 308
Hornykiewytsch, T., 307
Horowitz, H.B., 286
Hörstadius, S., 46, 48, 50
Horsten, G.P.M., 65, 70, 94, 476
Hort, W., 263
Hortenstine, J.C., 232, 239, 243
Horvath, A., 87, 88, 93
Horvath, S.M., 87, 88, 89, 91, 93, 232, 285, 373
Horwitt, M.K., 127
Hoshiko, T., 452, 525, 528, 529
Hosie, R.T., 191
Hosko, M.D., Jr., 92
Hosoi, K., 332
Hossack, J., 491
Hotovy, R., 72
Houck, C.R., 74
Hougen, O.A., 62
Houget, J., 475
Hough, J.M., 521, 522
Hough, W.H., 468
Hougie, C., 221
Housholder, D. E., 450
Houssay, B. A., 5
Houssay, H. E. J., 276
Houston, C. S., 153
Houten, J. C. van, 135
Hove, E. L., 129
Howard, A., 310
Howard, A. R., 374
Howard, J. M., 184, 191, 241
Howard-Flanders, P., 308
Howe, A., 476
Howell, D. S., 239, 246, 383
Howell, F. R., 260
Hower, J., 233
Howes, N. H., 350
Hoyle, G., 25, 343
Hrenoff, M. K., 502
Hsia, T. W., 381
Huang, K. C., 232
Hubay, C. A., 159, 374
Hubbard, S. J., 275
Huber, C., 60, 62, 74
Huber, P., 124
Hubner, K. A., 474
Huddlestun, B., 22
Hudson, G. W., 307
Hudson, M. T., 140
Hudson, R., 383
Huertas, J., 500
Huf, E. G., 18, 27, 529
Huff, R. L., 135, 231, 233, 234, 242, 243, 244, 271, 272, 285, 375
Hufnagel, C. A., 160, 267, 268, 281, 377, 383
Huggett, A. St. G., 17, 475
Huggins, C., 473
Huggins, R., 101
Huggins, W. H., 433
Hughes, A., 45
Hughes, C. H., 207
Hughes, F. A., 189
Hughes, F. B., 177
Hughes, J. R., 430, 433
Hughes, R. R., 504
Hughes Jones, N. C., 231
Hugh-Jones, P., 156
Huguenard, P., 85, 86, 97, 98, 100
Hukovic, S., 187
Hull, H. B., 157
Hultgren, H. N., 166, 381
Hultman, H. I., 163
Hume, D. M., 97, 404, 444, 445, 446, 448, 449, 468, 546
Humphrey, R. R., 48
Humphries, J. O'N., 383
Hung, L. V., 133
Hunnicutt, A. J., 183
Hunsperger, R. W., 501
Hunt, C. C., 497
Hunt, J. N., 410, 541
Hunter, F. E., 126, 131
Hunter, F. R., 72
Hunter, R. B., 210, 213, 214
Hunzinger, W. A., 23
Hurley, L. S., 473
Hurn, M., 220
Hurtado, A., 153, 233
Hussey, C. V., 208, 210
Huston, J. H., 263, 380
Huston, M. J., 140, 141
Hutt, B. K., 87, 88, 89, 91, 373
Hutter, O. F., 408
Huwald, R , 472
Huxley, A., 17, 25
Huxley, J. S., 83
Huycke, E. J., 22
Hyatt, R. E., 239, 246, 383
Hyde, G. M., 194, 231, 233, 234, 236, 238, 239, 242
Hyde, T. W., 423, 426
Hylin, J., 369
Hyman, C., 502
Hymans, J. C., 185
Hynes, H. B. N., 337

I

Iacobellis, M., 532, 533, 535, 537
Iampietro, P. F., 97
Iaroshevsky, A. J , 574
Iggo, A., 178, 410
Iglesias, R., 474
Iida, K., 476
Ikai, M., 499
Ikeda, Y., 406
Ikemoto, T., 448
Ikkos, D., 526
Ikushima, N., 45, 46
Iliev, I., 574
Imagawa, R., 477
Imai, K., 441
Imamichi, T., 470
Imparato, A. M., 410
Ingbar, S. H., 452
Ingelman-Sundberg, A., 474
Ingle, D. J., 439
Inglefinger, F. J., 192
Ingraham, R. G., 270
Ingram, G. I. C., 217
Ingram, M., 60
Ingvar, D. H., 494, 502
Inkley, S. R., 233
Inman, W. I., 86, 88
Inou, T., 441
Inui, H., 70
Iontov, A. C., 574
Ippolito, A., 477
Irving, I., 60, 61, 65, 66, 67
Irving, L., 83, 89
Isaacs, J. P., 158, 376
Isenburg, L. K., see Kich-Isenburg, L.
Isenschmid, H., 221, 222
Iseri, L. T., 542
Ishida, J., 46
Ishida, T., 189
Isley, J. K., 185
Ito, S., 47
Ivanova, T. C., 574

Ivanovic, H., 217
Iversen, P., 5
Ivy, A., 182
Ivy, A. C., 186
Izarn, P., 208

J

Jackson, D. P., 209
Jacob, M., 99
Jacobs, G. J., 207
Jacobs, G. S., 530, 538
Jacobs, H. I., 380
Jacobs, M. H., 63
Jacobs, W., 333
Jacobs, W., 333
Jacobsen, C. W. S., see Sem-Jacobsen, C. W.,
Jacobsohn, D., 447
Jacobson, H. N., 527
Jacobson, L. O., 244, 310, 311, 314
Jacoby, G. A., Jr., 402, 404
Jadrijevic, D., 473
Jaeger, C. A., 246
Jaeger, E. C., 83, 84
Jaenike, J. R., 242
Jaffe, H., 452, 457
Jaggi, A., 284
Jailer, J. W., 443, 444
Jaimet, C. H., 175
Jalavisto, E , 190
James, A. H., 542
James, F., 476
James, W. O., 141
Jamison, W. L., 167
Jancso, N., 350
Janeway, C. A., 240, 245
Janisch, E., 74
Jänkälä, E. O., 444
Janke, J., 126, 365
Janowitz, H. D., 192
Jansen, H., 301, 302
Jansen, J., 493, 496, 502
Janssen, S., 286
January, L. E., 91, 373
Jaques, L. B., 214
Jarausch, K. H., 30
Jaroslow, B. N., 319
Jasper, H. H., 489, 495
Jaster, R., 304
Jaulmes, C., 87, 89, 100, 101
Jauregui, R. H., 130
Jaynes, J., 405, 469
Jean, E., 91
Jefferson, G., 494
Jefferson, N. C., 179, 189, 265
Jeffords, J. V., 282
Jeffrey, M. R., 242
Jenden, D. J., 194
Jenkins, D., 439
Jenney, E. H., 128
Jennings, D., 183
Jennings, F. L., 303
Jennings, M. A., 182
Jennings, R. B., 528
Jensen, C., 84, 502
Jensen, C. E., 420
Jensen, E., 183
Jensen, E. V., 473
Jensen, H., 219, 453
Jensen, W. N., 234
Jenson, R. L., 529, 531, 533
Jentzer, A., 101
Jerger, J. F., 433
Jervell, K. F., 22
Jielof, R., 434
Jiménez-Vargas, J., 166
Jirka, J., 520
Jöchle, W., 468, 469, 475
Joekes, A. M., 545
Joels, N., 90
Johansson, B., 91, 373
Jöhl, A., 526
John, E. R., 503, 504
Johnels, A., 368
Johnsen, S. G., 471, 478
Johnson, C. W , 281
Johnson, C. G., 69
Johnson, F. H., 13, 15, 60, 61, 62, 70, 72, 73, 74
Johnson, G., 70
Johnson, G. R., 123
Johnson, I. S., 44, 367
Johnson, J. A., 20, 140
Johnson, J. F., 217, 218
Johnson, L. H., 22
Johnson, R. E., 476
Johnson, R. M., 476
Johnson, R. T., 239
Johnson, S. A , 207, 210, 211, 212, 216, 217, 219
Johnston, A. D., 163, 283
Johnston, D. H., 185
Jolles, B., 309
Jolly, H., 468
Joly, M., 361
Jonas, H., 23
Jones, C. M., 181, 182
Jones, J. C., 363, 404, 449, 503
Jones, L. L., 335
Jones, N. C. H., see Hughes Jones, N. C.,Jones
Jones, P. H., see Hugh Jones P.
Jones, R. M., 85
Jones, R. W., 152
Jongbloed, J., 86
Jongh, S. E. de, 470-471
Jonsson, B., 287
Joos, H., 65
Jordan, P. H., Jr., 190
Jørgensen, C. B., 27, 349, 350
Jorio, L., 86
Joseph, J. D., 270
Josephson, B., 31
Josse, J. W., 235
Jouve, A , 381
Jouvet, M., 94, 500
Joyce, C. R., 23
Jubb, K. V., 442
Juda, W., 19
Judd, O. J., 285, 375
Judson, C. L., 360
Judson, W. E , 246, 262, 285
Julain, L. M , 234
Julian, F., 153, 155
Julius, H. W., 131
Jullien, A., 361, 364
Jung, F., 72
Jungmann, H., 281
Jurado, M. D., 166
Jürgens, R., 207, 210, 218, 219
Jurka, J., 222
Jussila, R., 185
Juster, R., 270
Juvenelle, A., 85, 86, 99

K

Kaada, B. R , 496, 502
Kadetz, W., 166
Kahn, A., 166
Kahn, J. B., 125
Kahnt, F. W., 541
Kahny, H. M., 219
Kaiser, E., 285, 375
Kaiser, I. H., 476
Kakossaios, G , 31
Kaliampetsos, G., 208
Kallas, J., 31
Kalliomäki, L., 183
Kalman, S. M., 27, 473
Kalnitsky, G., 138
Kalser, M. H., 191
Kalter, H., 192
Kamakhya, P. M., 193
Kamer, J. H. van de, 185, 186
Kaminski, Z. 89
Kamijo, K., 135
Kamrin, B. B., 546
Kamrin, R. P., 51, 546
Kanai, J., 448
Kandel, A., 138
Kanter, D. M., 246, 520
Kanter, G. S., 547
Kanter, S. L., 190
Kanungo, M. S., 360
Kao, C. Y., 20, 32
Kao, F. F., 154, 155
Kaplan, B., 475
Kaplan, H. S., 310, 315, 317, 318, 319
Kaplan, N. O., 133, 136
Kaplan, S. A., 527
Kaplan, W. D., 303, 309
Kapterev, P., 67
Kar, A. B., 477
Karachi, H. H., 92
Kark, R. M., 240, 514
Karlberg, P., 166, 233
Karli, P., 469
Karli, P., 400
Karmea, A., 380
Karnofsky, D. A., 46
Karnosh, L. J., 494
Karpeles, L. M., 242, 271

Karpeles, L. M., 242, 271
Karsh, M. L., 122
Karvinen, E., 186
Karvonen, M. J., 17, 475
Kasanen, A , 182
Kass, G. H., 86
Kassenaar, A. A. H., 471
Katchalski, E., 216
Katsuki, S., 406, 448
Katsuki, Y., 421, 432, 434
Katsura, S , 98, 99, 402
Kattus, A. A., 161
Katz, A.M., 379
Katz, B., 61, 72, 371
Katz, L. N., 263, 268, 277, 283, 378, 379, 383
Kaufman, A. A., 411
Kaufman, B. N., 377
Kaufman, D., 282
Kaufman, N., 192, 477
Kaufmann, C., 473
Kaufmann, G., 285
Kauntze, R., 177
Kavanu, J. L., 69
Kawai, T., 449, 451, 468, 469
Kawakami, I., 41, 42
Kawakami, M., 475
Kay, J., 545
Kay, R. H., 166
Kayser, C., 83-120; 83, 84, 85, 87, 88, 89, 90, 91, 92, 93, 94, 97, 99, 100, 102
Kayser, D., 101
Kearns, W. M., 477
Keating, J. H., 154, 246, 520
Keeton, R. W., 235, 457
Kehne, J. H., 189
Keidel, W. D., 425, 433, 434
Keitzer, W. F., 270
Kékesi, F., 406, 576
Kekwick, R. A., 217
Kelemen, I., 99
Kelemen, K., 581
Kelentei, B., 409
Kellaway, C. H., 72
Keller, A. D., 447
Keller, M. R., 404, 468
Kellerman, G. M , 477
Kelley, B., 307
Kellogg, R.H., 527
Kelly, J. J., Jr., 188
Kelner, A., 65
Kelsey, W. M., 262, 519
Keltch, A. K., 132
Kemény, T. T., 192
Kemp, C., 452
Kemp, E. H., 430
Kemper, F., 276, 284
Kemph, J., 283
Kennamer, R., 371
Kennard, M. A., 502
Kennedy, R. L., 264
Kennedy, V. E., 96
Kenny, J., 210
Kepes, J., 166
Kereiakes, J. G., 315
Kernan, R. P., 26
Kerpel-Fronius, E., 99
Kertai, P., 91
Kerr, A. C., 444
Kerr, D. I. B., 491, 492
Kesert, B. H., 499
Kessler, M. M., 405, 496
Kessler, W. B., 449
Kesztyüs, L., 266
Kettenborg, H. K., 209
Kety, S. S., 264
Kewitz, H., 136
Keynes, R. D., 13, 17, 18, 20, 25, 26
Keys, A., 245
Keys, A. B., 346
Khabarova, A. J., 574
Khalil, H. H , 86
Khanin, N., 574
Khrolinsky, L. G., 559
Khvoles, G. J., 562
Kidd, B. S. L., 258
Kidokoro. M., 471
Kilb, R. H., 287
Killam, K. F., 380
Killion, P. J., 491
Kilpatrick, R., 261
Kim, C., 399, 401, 501, 502
Kim, K. S., 184, 185, 270
Kimball, D. M., 212
Kimball, R. F., 309
Kimelblot, S., 268, 283, 378
Kimura, R., 491
Kimura, Y., 306
Kind, L. S., 86
King, C. G., 133
King, E. E., 494, 496
King, E. R., 232, 233
King, H. E., 501
King, J. T., 384
King, P. D., 221
King, R. B., 492
King, T. J., 48
Kingsley, C. S., 219
Kinney, T. D., 192, 477
Kinsell, B. G., 211, 212, 219
Kinsell, L. W., 183
Kinsella, R. A., 473
Kinter, W. B., 262, 516, 517, 518
Kipfer, K., 20
Kirchberg, H., 306
Kirikae, I., 433
Kirk, P. L., 320
Kirkendall, W. M., 457
Kirkman, H., 477
Kirkwood, J. G., 19
Kirrman, J. M., 47
Kirschner, L. B., 18, 27
Kirsner, J. B., 181
Kisch, B., 97, 366, 373
Kiss, É., 519
Kiss, G. T., 154, 537, 539
Kitchell, R. L., 443
Kitching, J. A., 320, 321, 333
Kjelberg, S. R., 287
Kjellberg, S. V., 234
Klakeg, C. H., 372
Klatskin, G., 190
Klavins, J. V., 192, 477
Klebanoff, S. J., 141
Kleeman, C. R., 93, 235, 526, 5 529, 531, 533, 539
Kleeman, H., 166
Klein, D., 44
Klein, D. E., 283
Kleinerman, J., 263, 264, 284
Kleinfeld, G., 216
Kleinfeld, M., 372
Kleinschmidt, H. J., 456
Kleinsorg, H., 241
Klepping, J., 100
Klepzig, H., 376
Kline, E. W., 384
Kline, I. T., 473
Kling, A., 400
Klingenberg, H. G., 271
Klingerman, M. M., 305
Klinke, J., 67
Klopper, P. J , 181, 267, 405
Klosovsky, B. N., 579
Klüver, H., 501
Knapp, F. M., 502
Knigge, K. M., 442, 470, 471
Knight, P. F., 44
Knipping, H. W., 157
Knisely, M. H., 282
Knobil, E., 443
Knock, G. G., 73
Knocker, P., 520
Knoll, J., 581
Knöpfelmacher, F., 93
Knowles, J. H., 161
Knowles, J.L., 375
Knowlton, A. I., 439
Knowlton, K., 406
Knox, R., 131
Knox, W. E., 141
Koch, D., 264
Koch, H., 347, 348
Koch, H. J., 30, 336, 337, 340
Koch, R., 301, 305, 308
Koch, W., 473
Kochakian, C. D., 478
Koch-Isenburg, L., 83, 87
Kocsár, L., 266
Koda, F., 131
Koehm, C. J., 175
Koella, W. P., 94, 400, 494
Koelle, E. S., 123
Koelle, G. B., 135
Koepchen, H.-P., 157
Koetschet, P., 100
Köhler, V., 123
Köhler, W., 495
Koikegami, H., 400
Koizumi, K., 95, 492, 497
Kojima, T., 405
Kok, K., 208
Kokas, E., 378
Kokas, F., 91
Koketsu, K., 492
Kolder, H., 153, 163
Kolderie, M. Q., 50

Kolendic, M., 84
Koletsky, S., 283, 451, 542
Kolff, W. J., 519
Koller, F., 205, 213, 214, 222
Koller, G., 469
Kolsky, M., 100
Koltay, E., 547
Komarov, S. A., 191
Kominz, D. R., 215
Konecci, E. B., 307
Konigsberg, I. R., 45
Konigsberg, U. R., 46
Koopman, L. J., 65, 70, 94
Kopeloff, L. M., 500
Kopeloff, N., 500
Koppel, J. L., 208
Koppermann, E., 100
Korman, H., 282
Korner, A., 478
Kornfeld, P., 524
Korst, D. R., 183
Körtge, P., 239, 240
Kortsak, A. S., see Sass-Kortsak, A.
Kory, R. C., 91
Kosaka, K., 69
Koscak, M., 136
Kosel, G., 475
Kosenko, T. M., 576
Koskelo, P., 380
Koskimies, J., 83
Koskoff, Y. D., 500
Kosman, M. E., 275, 410
Kossmann, C. E., 371
Kosterlitz, H. W., 370
Kostial, K., 95, 408
Kostuk, D. S., 562
Kostuk, P. G., 560
Kotanová, E., 520
Kough, R. H., 162
Koulagin, B. K., 576
Kovách, A. G. B., 547
Kovach, J., 271
Kovach, J. C., 167
Kowalewski, K., 181
Kowalski, H. J., 240
Krakauer, L. J., 182, 439
Krakusin, J. S., 528
Krall, J., 268
Kramar, J., 271
Kramar, M. S., see Simay-Kramar, M.
Kramer, J. G., 526
Kramer, K., 87, 261
Kramer, P., 177
Krantz, J. C., Jr., 384
Krassousky, V. K., 571
Kraupp, O., 21
Krayer, O., 370
Kream, J., 369
Krebs, A. A., 139
Krebs, A. T., 307, 315
Krebs, H. A., 365
Kreezer, E. H., 59, 70
Kreezer, G. I., 59, 70
Kreindler, A., 566
Krejci, F., 434
Krenkel, W., 94, 101
Kreuziger, H., 284
Kriagev, V. J., 583
Krieg, H., 83
Krieg, J., 383
Krieg, W. J. S., 430
Krieger, H., 233
Krieger, H. P., 492
Krijgsman, B. J., 95, 345, 359, 360, 364
Krijgsman-Berger, N. E., 359
Kristiansen, K., 127
Krivanek, J. O., 50
Krnievíc, K., 24
Kroeker, E. J., 279
Krog, H., 89
Krog, J., 89
Krogh, A., 4, 10, 329, 330 332, 333, 335, 336, 337, 338, 339, 343, 344, 345, 346, 349, 351, 353
Krogsgaard, A. R., 521, 547
Krohmer, J., 189
Krohn, P. L., 473
Kroll, F. W., 86
Kronen, P. S., 383
Krop, S., 369
Krosch, H., 282
Krostev, K., 574
Krueger, A. P., 73
Kruesi, O. R., 537, 539
Kruger, L., 495, 500
Kruhöffer, P., 22
Krum, A. A., 47
Krumins, R. F., 504
Kruse, R., 126
Kruse, W. T., 139
Kruta, V., 91
Kryder, G. D., 305
Kucsko, L., 468
Kuffler, S. W., 491, 498
Kugelen, B. von, 87
Kuhl, W. J., Jr., 93, 96
Kuhn, W., 29
Kühns, K., 372
Kuida, H., 158, 161, 269
Kuiper, J. W., 434
Kullander, S., 472
Kun, E., 128
Kundratitz, K., 222
Künkel, H. A., 304
Kunlin, J., 87, 100
Kuntz, A., 410
Kuperman, A. S., 136
Kupperman, H. S., 449
Kuramoto, K., 372
Kurients, E., 444
Kurosawa, M., 468
Kurotsu, T., 440
Kurtz, I., 51
Kurtzin, I. T., 571
Kuru, M., 492
Kuschinsky, G., 122
Küster, E., 70, 74
Kuusisto, A. W., 179
Kuzin, A. M., 307
Kwaan, H. C., 217
Kyle, J., 179
Kyle, R. H., 457

L

Laake, H., 532, 533, 534
LaBarre, J., 383
Laborit, H., 85, 87, 100, 101
Labrousse, Y., 154
Lacassagne, A., 305, 307
Lachiver, F., 85, 87, 96
Lackner, R., 217
Lacy, W. W., 285, 375
Ladd, M., 522
Ladman, A. J., 470, 475
Ladopoulus, C., 91
LaDue, J. S., 380
Laforet, M. T., 243
La Franca, S., 97
Lagerlöf, H. O., 161, 285
Laget, P., 93
Lagoutina, N. I., 578
Lahti, R. E., 370
Laidlaw, J. C., 439
Laidler, K. J., 61, 62, 63, 134
Lainé, P., 86
Lairy, G. C., 500
Lajthe, A., 68
Lake, B., 190
Lakhanpal, M. I., 66
Laki, K., 211, 215
Lakomkin, A. I., 287
L'Allemand, H., 100, 165, 283
Lallemand, S., 73
Lamanna, C., 75
Lamarche, M., 235
Lambert, G., 303, 306, 307, 308, 314
Lambert, G. F., 195
Lambert, P.-P., 523
Lambertsen, C. J., 162
Lamdin, E., 529, 530, 531, 533
Lamerton, L. F., 303, 314
Lameyer, L. D. F., 456
Lammerant, J., 237, 272
Lanchantin, G. W., 210, 219
Landau, J., 60
Landau, R. L., 178
Landgren, S., 498
Landis, E. M., 232, 239, 243, 284
Landor, J. H., 180
Landowne, M., 284, 286, 383
Lane, N., 187
Lang, S., 545
Langdell, R. D., 211
Langdon, R. G., 138
Lange, G., 122
Lange, J., 244
Langemann, M., 124
Langendorf, P., 369
Langendorff, H., 301, 305, 308
Langham, W. H., 309
Langmuir, I., 3, 63
Lanphier, E. H., 162
Lanzavecchia, G., 45
Lanzing, W. J. R., 348

Lapina, I.A., 570
Laporte, Y., 491
Laqueur, G.L., 403, 404, 406, 447, 467
Laragh, J.H., 542
Lardy, H., 132, 133
Laroche, M.F.M., see Mours Laroche, M.F.
Larrabee, M.G., 407
Larrieu, M.J., 207, 212
Larson, F.C., 175
Larsson, S., 403
Lasch, H.G., 213
Lasher, E.P., 232, 234
Lashof, T. W., 286
Lasker, N., 380
Lasker, S.E., 242
Lassen, N.A., 262, 515, 516
Lasser, E.C., 306
Lasser, R.P., 281, 371
Latarjet, R., 64, 299, 300
Lathem, W., 524
Latmanisova, L.V., 558
Latorre, G., 548
Latour, H., 372
Latour, J.P.A., 471
Latts, E.M., 179
Lau, F. Y. K., 231, 238
Laufberger, V., 86
Laufman, H., 88
Laughton, R., 183
Laur, C. M , 97
Laurell, G., 306
Laurent, D., 263
Lauson, H. D . 240
Lavenda, N., 96
Lavietes, P. H., 244
Lavigne, S., 100
Lavik, P. S , 130
Lawdowicz, W., 207
Lawn, A. M.. 407
Lawrence, J. H., 231, 233, 234, 235, 238, 239, 241, 242, 244
Lawrence, L. H., 452
Lawrence, M., 417, 420, 424, 425, 427, 433, 434
Lawrow, J. W., 87
Laws, J. O., 309
Lawther, P.J., 93
Lawton, R.W., 278, 279
Lazar, J., 300, 303, 304, 305, 306, 307
Lazaro, E.J., 239
Lazarte, J.A., 500
Lea, D.E., 299, 300
Leaf, A., 125, 141
Leathart, G.L., 166
Leathem, J.H., 471, 477
Lebedev, A.A., 576
Le Bihan, H., 303
Lebowitz, W.B., 132
LeBrie, S.J., 403, 447, 527
Lechner, G., 126
Lechtenbörger, H., 159, 269
Leckie, F.H., 472
LeClerq, J., 48
Lecomte, J., 208, 303
LeCompte, P.M., 457
Lecoq, R., 405
Lederer, M.E., 380
Ledingham, I.C., 333
Ledoux, L., 48
Lee, C.C., 536
Lee, F., 50
Lee, G. de J., 158, 242, 269
Lee, J.S., 270
Lee, K. S., 123, 125
Lee, N.D., 453
Lee, P.R., 184
Lee, R.C., 83
Lee, S.L., 219
Lee, S. van der, 469
Lee, Y.C.P., 384
Leeds, S.E., 86
Leeuw, J. de, 102, 449
Leduc, E.M., 84
Lehninger, A.L., 133
Lehr, H., 100
LeFevre, P.G., 13, 16
Legge, J.W., 60
Leggett, J.E., 16
Legouix, J.P., 417, 424, 425, 426, 434
Lehman, H.E., 50
Lehmann, F.E., 51
Lehmann, G., 284
Lehotsky, P., 74
Leiberman, D.M., 469
Leifer, E., 524
Leiter, L., 525, 526, 537
Lele, P.P., 490
Lemaitre, M., 94
Lemberg, R., 366
Lemley-Stone, J., 380
Lemonnier, A., 213, 219
Lemorgne, S., 71
Lenahan, J.G., 208
Lennep, E.W. van, 95
Lennox, M.A., 491, 495
Leonard, E., 534, 535
Leonardi, M.C., 45
Leone, C.A., 44, 367
Leone, E., 477
Leonhardt, H., 440
Lepercq, C., 239, 240
Lequime, J., 262
Lerner, R., 384
LeRoy, G.V., 231
Lesse, H., 399
Lessen, M., 281
Letandre, P., 210
Lettvin, J.Y., 410, 496
Leuchtenberger, C., 47
Leupold, R., 209
Leusen, I., 268, 269, 378
Lev, M., 384
Levassort, C., 102
Levedahl, B.H., 478
Levenbook, L., 342
Lever, J.D., 472
Lever, W.F., 271
Levey, H.A., 133, 477
Levey, S., 233
Levi, H., 27, 350
Levi-Montalcini, R., 49
Levin, J., 474
Levin, M.E., 457
Levine, P., 232
Levine, R., 22, 132
Levine, R.B., 371
Levine, S., 182
Levine, S.A., 371
Levine, S.L., 188
Levinger, E.L., 526
Levinsky, N.G., 350
Levinson, D.C., 189
Levitina, G.A., 559
Levitt, J., 73
Levitt, M.F., 244, 536
Levitz, M., 475
Levy, A.H., 182
Levy, J., 410
Levy, L., 126
Levy, M.N., 260, 277, 373
Levy, R.S., 403
Levycky, N.V., 443
Lewin, I., 60, 70, 74
Lewis, A.E., 178, 309
Lewis, B.M., 264
Lewis, D.H., 283
Lewis, F.J., 85, 88
Lewis, G.P., 175
Lewis, J., 210
Lewis, J.A., 521
Lewis, O.J., 260
Lewis, P.R., 494
Lewis, S.E., 136
Lewis, P.M., 183
Lewis, Y.S., 218
Li, C.-L., 489, 494, 495
Li, C.H., 245, 276
Ley, A.B., 243
Li, M.C., 454, 526
Li, T.H., 160
Liakopoulus, P., 100
Lian, C., 91
Liberson, W.T., 557-88; 399, 501
Libert, R., 476
Libet, B., 94
Lichstein, H.C., 131
Lichtman, H.C., 183
Licklider, J.C.R., 427, 433
Liddle, G.W., 541
Liddle, L., 522
Lidicker, W.Z., 236
Lidicker, W.Z., Jr., 91
Lidz, T., 456
Liébecq, C., 141
Lieberthal, M.M., 188
Liedke, K.B., 43, 46
Lifson, N., 233
Lilienfield, L.S., 262, 515, 516
Liljegren, E.J., 307
Liljestrand, G., 1-12; 176 491
Lillehei, C. W., 238
Lilly, J.C., 432
Lilly, S.J., 30, 332

Lim, T.P., 154
Lin, E.C.C., 141
Lin, T.M., 186
Lind, A.H., 124
Lind, J., 85, 86, 99, 233, 475
Lindahl, P.E., 61, 474
Lindblom, U.F., 496
Linden, R.J., 372
Linderholm, H., 18, 27, 154, 164
Lindgren, L., 165
Lindgren, P., 260, 275, 276, 406
Lindholm, A., 236
Lindner, A., 280
Lindsay, W.K., 87, 90, 91, 100
Lindsey, A.W., 377
Lindsley, D.L., 319, 320
Lineweaver, H., 134
Ling, G., 14, 15, 69, 503
Ling, P.C., 85, 93
Linhart, J., 260
Linko, E., 380
Linquette, Y., 372, 381
Linzell, J.J., 140
Lipman, C.B., 66
Lipmann, F., 133
Lipmann, M., 133
Lipsett, M.B., 454, 526
Lipschutz, A., 473, 474
Lison, L., 477
Lissák, K., 406, 407, 565, 576, 581
Litter, J., 281
Little, J.M., 262, 519
Liu, C.-N., 491
Livingston, R.B., 399, 495, 496, 499
Ljungberg, E., 187
Lloyd, D.P.C., 497
Lobanova, L.B., 574
Lobashev, M.E., 575
Lockwood, W.H., 366
Lockyear, W.H., 166
Loder, J.W., 132
Loeb, L., 270
Loeb, R.F., 96
Loefer, J.B., 70
Loeser, A., 474
Loewenstein, W.R., 408
Loewi, O., 372
Lofts, B., 477
Logan, J.S., 179
Logothetopoulos, J., 524
Lokhorst, W., 84
Loll, H., 123
Lombard, E.A., 372
Lomonos, P.I., 570
London, J., 180
Long, C.N.H., 440, 445, 449
Long, J.A., 140
Long, L.A., 210
Longinotti, L., 17
Longo, V.G., 101
Longson, D., 525, 540, 547
Loomis, T.A., 123, 140, 369
Loomis, W.F., 67
Lopatina, N.G., 579
Lorand, L., 211, 215
Lorber, V., 125, 366
Lorch, I.J., 48
Lord, J.T., 503
Lorenz, E., 310, 316
Lorenz, K., 83
Lorenz, N., 454
Loring, W.E., 234
Lothe, F., 308, 309
Lotspeich, W.D., 539, 540
Lott, J.R., 16
Loubatiéres, A., 122, 273
Lougheed, R., 178
Lougheed, W.H., 85, 92, 93
Loughridge, R.H., 233
Louis-Bar, D., 262, 519, 545
Loutit, J.F., 316, 318, 319, 320
Love, A.H., 259
Love, I.H., 60
Love, W.D., 23
Love, W.E., 24
Lovelock, J.E., 68, 88, 89
Løvtrup, S., 45, 321
Lowenstein, B.E., 125
Lowenstein, O., 433
Löwgren, E., 524
Lown, B., 371
Lowry, O.H., 126, 131, 418, 420
Lowy, K., 430
Lubinska, L., 95
Lucas, V., 47
Luchsinger, E.B., 544
Luck, C.P., 28
Luck, J.M., 245
Lucké, B., 28
Luckner, H., 71
Lucot, M.A., 84, 87, 89, 91, 92, 99
Ludany, G., 91
Ludes, H., 157
Luduena, F.P., 362
Luetscher, J.A., Jr., 243, 246, 541, 542
Luft, R., 526
Luft, U.C., 156, 163, 164
Lühning, I., 157
Luisada, A. A., 166, 378
Lüllmann, H., 125, 367
Lundberg, A., 47, 74, 93, 491
Lundberg, U., 444
Lundegårdh, H., 16
Lundin, G., 157
Lurie, R.N., 568
Lüscher, E., 211
Luthy, E., 281
Lutwak-Mann, C., 472
Lutz, H., 48
Lutz, W., 88, 89, 93
Luyet, B.J., 65, 66, 68, 70, 73, 74
Lybeck, H., 92, 262, 519
Lyman, C.P., 84, 89, 92, 94, 95, 453
Lynch, J.R., 447
Lynch, P.R., 286
Lynn, R.B., 87, 91
Lyon, E.S., 180
Lyon, M.F., 49, 303, 309
Lyons, R., 503
Lyons, R.N., 217
Lyons, W.R., 140, 476

M

Maaske, C.A., 153, 159
McAllen, P.M., 384
McAuliffe, D., 427, 428
McBirnie, J.F., 92
McCall, M.S., 231
McCann, S.M., 401, 402, 403, 404, 406, 447, 448, 449, 450, 467, 502
McCarthy, E.F., 245
McCarthy, J.F., 133
McCarthy, R.E., 188
McCarver, C.T., 515
McCawley, E.L., 370
Macchi, G., 501
Macchi, I.A., 282
McClenahan, J., 161
McClenathan, J.E., 232, 233
McClure, C.C., 494
McConnell, K.P., 234
McCormick, W.G., 306, 307
McCoubrey, A., 128
McCouch, G.P., 492, 499
McCrory, C.B., 374
McCubbin, J.W., 152, 273, 274, 275
McCulloch, W. S., 496
McCulloh, E. F., 307
McDermott, W. V., 449
McDonald, D. A., 280, 286
MacDonald, E., 70
Macdonald, I., 166, 180
McDonald, I. R., 444, 446, 449
McDonald, J. E., 305
McDonald, J. H., 478
McDonald, R. K., 451
MacDonald, W. B., 526
McDowall, R. J. S., 21, 385
McDowell, M., 246
McElroy, W. D., 74, 127, 503
McEntee, K., 442
McEwen, L. M., 407
McFadyean, A. J. S., 217
Macfarlane, R. G., 209, 220, 221
Macfarlane, W. V., 91
McGarry, E., 523
McGeer, K., 74
McGubbin, J. W., 409
Mach, E., 444
Mach, R. S., 541, 542
Machebouf, M., 131
McHenry, E. W., 133
Macher, E., 261
Machne, X., 399, 498, 501
McIlroy, M. B., 156
McIlwain, H., 503, 504
McIlwain, M., 129

MacIntosh, F. C., 407
McIntyre, A. K., 497
MacIntyre, I., 529, 531
Macintyre, M. N., 472
MacIntyre, W. J., 233
Mack, H. C., 476
McKay, D. G., 188, 208
McKay, E. A., 93
Mackay, I. F. S., 261
Mackay, I. R., 186, 245
Mackay, M. E., 217
MacKeith, R. C., 86
McKenzie, B. F., 211, 212
Mackenzie, K. A., 306
MacKenzie, W. C., 181
McKerrow, C. B., 156
McKinley, S. H., 312
MacKinnon, I. L., 476
MacKinnon, P. C. B., 476
McKusick, V. A., 384
McLardy, T., 398, 501
MacLean, J. P., 454, 526
MacLean, P. D., 397-416; 398, 399, 401, 501, 502
McLendon, W. W., 211
McLennan, H., 10, 14, 15, 338, 407, 503
MacLeod, M. B., 529, 530, 531, 532, 533, 543
MacMartin, M. P., 245
McMaster, R. D., 45
McMillan, G. C., 306
McMillan, I. K. R., 87, 91, 383
McMorris, R. O., 281
McMullen, M., 519
McMurrey, J. D., 97, 189, 445
McNamara, B. P., 135
McNeely, W. F., 240
McNickle, C. M., 187
Macpherson, R. K., 256
McQueen, D. A., 93
MacQuigg, R. E., 156
MacRae, G. D. E., 306
McSwiney, R. R., 439
Madden, R. F., 89
Mader, I. J., 542
Madlafousek, J., 260
Madow, B., 282
Madsen, A., 491, 495
Maegraith, B. G., 189, 265 266
Maengwyn-Davies, G. D., 471
Magee, D. F., 190, 191
Magendie, M. J., 474
Magin, J., 372
Magliocca, R., 86
Magni, F., 501
Magnusson, A.-M., 473
Magoun, H. W., 85, 305
Mahler, H. R., 366
Maier, A., 86, 100, 102
Maier, E., 86
Maier, K., 545
Main, R. K., 312, 313
Maire, F. W., 182, 401, 402
Maisin, H., 303, 304, 305, 306, 307, 308, 309, 310, 312, 314
Maisin, J., 303, 304, 305, 306, 309, 310, 312, 314
Maizels, M., 22, 23
Makarenko, L., 272, 383
Makinodan, T., 319, 320
Makler, J., 28
Makowski, E. L., 476
Malagamba, G., 217
Malamud, B., 370
Malandra, B., 468
Malcolm, J. L., 95
Maldague, P., 303, 305, 309, 310, 314
Malim, A., 93
Malin, A., 236
Malinovsky, O. V., 582
Malinow, M. R., 370
Malis, L. I., 495
Malizia, E., 517, 518
Mallov, S., 366
Malm, M., 180, 475
Malméjac, C., 91, 94, 95, 97
Malméjac, J., 90, 94, 95, 97, 100, 101, 277, 407, 408
Malmendier, C., 523
Malmo, R., 499
Malmström, G., 157, 376
Maloney, M., 210
Malorny, G., 101
Maltez, J., 383
Malvin, R., 540
Malý, V., 241
Mammen, E., 213
Man, E. B., 240, 245
Manai, G., 208
Mancuso, V., 46, 50, 51
Mandart, M., 303, 306, 307, 308, 314
Manuel, M. J., 270, 375, 515, 522
Mandel, P., 304
Mandelbrote, B. M., 456
Mandema, E., 183
Mandl, A. M., 471
Manery, J. F., 21
Mangold, O., 49
Mangold, R., 264
Manigla, R., 264
Manly, B. M., 84
Mann, C. L., see Lutwak-Mann, C.
Mann, F. D., 205-230; 220
Mann, T., 477
Mannheimer, E., 287
Manning, P. R., 209
Mannix, E. P., 281, 375
Mansson, B., 137
Mantecchini, P., 86
Marberger, E., 132
Marceron, L., 89
Marchand, N., 371
Marcovic, L., see Markovic-Giaja, L.
Marcus, A., 138
Marcus, E., 545
Mardones, E., 473, 474
Marenina, A. I., 566
Margaria, R., 166
Marine, D., 456
Marini, M., 378
Marinosci, A., 477
Marinsky, J. A., 19
Markee, J. E., 468
Marko, A., 501
Markovic-Giaja, L., 84, 85, 87, 89, 96, 98
Marks, B. H., 137
Marks, E. K., 310, 311, 314
Marks, P. A., 241, 267
Markus, G., 233
Marlier, G., 71
Marmorston, J., 233, 367, 403, 449, 524
Marois, M., 89, 98, 102
Marro, F., 166
Marrone, L. H., 23
Marsh, B. S., 343
Marsh, F., 475
Marsh, J. B., 366
Marshall, A. J., 477
Marshall, E. K., 346
Marshall, H., 157
Marshall, J., 374
Marshall, J. M., 372
Marshall, L. H., 271
Marshall, N. B., 402
Marshall, R., 165, 192
Marshall, W. K., 469
Marshall, W. H., 128
Marsland, D., 60, 73
Marson, F. G. W., 545
Martin, A. W., 70, 140, 141
Martin, C. J., 157
Martin, G., 89, 474
Martinelli, M., 378
Martinet, J., 475
Martinez, C., 468
Martini, L., 403, 451, 455, 468
Martius, C., 133
Marty, A., 140
Marullax, P. D., see Ducheme-Marullax, P.
Maruyama, K., 46
Masaya, A., 400
Maselli, F., 375
Mashford, M. L., 185
Mason, J. W., 400
Mason, W. A., 98
Masuda, H., 98, 99
Massart, L., 134
Massion, W., 161
Massman, W., 166
Massopust, L. C., Jr., 94, 402
Massullo, E. A., 160, 267, 268, 377, 383
Massumi, R. A., 372
Mastboom, J. L., 476
Masuoka, D. T., 125
Matallana, A., 370
Mateer, F. M., 242
Mathieu, H., 218
Matson, J. R., 83

Matsumoto, T., 402
Matter, M., 213, 214, 222
Matthews, R. E. F., 131
Matthews, R. J., Jr., 408
Matthews, S. A., 347
Matton, G., 275
Mattson, S. B., 159
Mauche, J., 273
Maude, D. L., 524
Maurat, J.-P., 372
Maurer, H., 306
Maurice, A., 99
Maurice, D. M., 28
Maury, P. B., see Bonet-Maury, P.
Maxwell, G. N., 380
Maxwell, R. A., 277, 447
May, R. M., 314
Mayer, G., 475, 476
Mayer, J., 84, 86, 193, 402
Mayer, S. E., 128
Mayerson, H. S., 242, 270, 271
Maynard, D. M., Jr., 359, 361
Mazia, D., 132
Mazoué, H., 94, 95, 100, 405
Mazzuoli, G. F., 477
Mead, J., 156, 165, 269
Mead, M., 502
Meagher, J. N., 492
Mechelke, K., 281
Meda, E., 91
Medawar, P. B., 65, 67
Mednicoff, I. B., 208
Medvedeva, N. B., 559
Meesman, W., 380, 383, 384
Mefferd, R. B., Jr., 70
Meilman, E., 370
Meineke, H. A., 244
Meirowsky, A. M., 94
Meiselas, L. E., 246
Meites, J., 476
Mell, A., 140
Mellanby, K., 69
Mellette, M. F., 75
Mellinkoff, S. M., 175-204; 194, 195
Melloni, G., 470
Melon, J. M., 101
Melroe, D. G., 91
Melrose, D. G., 87
Melton, C. E., Jr., 472
Melzack, R., 492
Mendel, D., 21, 385
Mendelow, H., 500
Mendelsohn, M. L., 543
Mendelson, C. E., 384
Mendelson, J., 127, 503
Mendenhall, J. T., 157
Mendez, R., 369
Mendlowitz, M., 243, 246
Meneely, G. R., 91, 380
Meng, H. C., 191
Menguy, R. B., 190
Menning, C. M., 166
Meot, R., 314
Mercier, J., 361
Mercier-Parot, L., 404
Meriel, P., 101, 515
Merino, M. C., see César Merino, M.
Merklen, F. P., 372
Merkoulova, O. S., 575
Merlen, J. F., 122
Meroney, W. H., 371
Merrill, A. J., 520, 547
Merrill, J. M., 380
Merrill, J. P., 545, 546
Merritt, H. H., 407
Merton, P. A., 489, 496
Mersheimer, W. L., 183, 242
Meschan, I., 307
Mess, B., 448
Messinger, N., 187
Mester, A., 99
Mestler, G. E., 477
Metcalfe, J., 268, 284, 475
Metras, H., 85, 86
Mettinen, M., 96
Mettler, F. A., 496
Metuzals, J., 439, 468
Metz, B., 83, 94, 152, 407
Metz, D., 261
Metz, D. B., 272
Metz, G., 314, 318
Meulders, M., 373, 409
Meyer, D. K., 93, 366
Meyer, J., 181
Meyer, J. S., 502
Meyer, R. K., 470, 475
Meyers, F. H., 239
Meyers, J. D., 264, 265, 267
Meyers, L., 210
Meyers, S., 372
Meyers, V. W., 271
Mialhe-Voloss, C., 447
Michael, S. T., 469
Michel, R., 132
Michel-Ber, E., 410
Michon, J., 306
Mickelsen, O., 245
Mickle, W. A., 399, 400, 430, 431, 433
Miczban, I., 378
Middlesworth, L. van, 453
Mietkiewski, E., 275
Mifune, S., 41
Migeon, C. J., 443, 444, 478
Mihailovic, L., 495
Mikkelson, W. P., 189
Mikulicz, K., 474
Mikulski, J. S., 70
Milch, E., 381
Miledi, R., 370
Miles, B. E., 90, 242
Millar, F. K., 29
Millar, G. J., 214
Millar, R. H., 363
Millen, J. W., 502
Miller, B. F., 545
Miller, C. L., 318, 319
Miller, D. G., 16
Miller, D. R., 184
Miller, D. W., 444
Miller, E. C., 132
Miller, F. S., 89, 97
Miller, G. J., 449
Miller, H. C., 166
Miller, J., 282
Miller, J. A., 132
Miller, J. A., Jr., 89, 97
Miller, K. D., 215
Miller, L. L., 130, 133
Miller, M. A., 87
Miller, P. H., 433
Miller, R., 237
Miller, R. D., 157, 159
Miller, R. E., 500
Miller, R. M., 152, 154
Miller, W. H., 399
Miller, Z., 134
Millican, R. C., 241, 242, 245, 283
Millichap, J.G., 129
Millikan, G.A., 234
Mills, E.L., 231
Mills, I.H., 439
Mills, J.N., 525, 540, 547
Milne, M.D., 529, 531
Milne, W.L., 312
Milstone, J.H., 215, 216
Milton, G.W., 187, 410
Miminoshvili, D.I., 559
Miner, N., 495
Minett, F.C., 84
Minganti, A., 47, 50
Minute-Sorokhtina, I.P., 561
Minz, B., 405, 486
Mirand, E.A., 306
Miravet, L., 409
Mirsky, I.A., 126
Mischel, W., 306
Mishkin, M., 500, 502
Mislin, H., 70
Mitchell, G.A.G., 406
Mitchell, G.W., 520, 547
Mitchell, J.S., 299, 309
Mitchell, K.G., 188
Mitchell, P., 29
Mitchell, W., 503
Mithoefer, J.C., 154
Mitidieri, E., 129, 134
Mitra, N.L., 499
Mizuno, H., 476
Mizuno, T., 47
Mnoukhina, R.S., 562
Moberger, G., 472
Mochizucki, M., 409
Mochizuki, M., 152, 157, 166, 275
Modern, F.W.S., 513
Moehlig, R.C., 526
Moeller, J., 262
Moir, T.W., 233, 238
Moisseiva, N.A., 575
Mollica, A., 406, 489, 493
Mollison, P.L., 67, 231, 232, 240
Molyneux, L., 166
Moncrieff, R.W., 491
Money, W.L., 47

Monge, C., 235
Monge, C.C., 283
Monkhouse, F.C., 218
Monnier, M., 399, 501
Monod, J., 61
Monod, R., 281
Monroe, R.R., 399, 400
Monroy, A., 44, 47
Monson, M., 89
Montalcini, R.L., see Levi-Montalcini, R.
Montemurro, D.G., 402
Montgomery, A.V., 177, 410
Montgomery, C.H., 139
Montgomery, H.F., 258, 261
Montgomery, M.M., 235
Montgomery, V., 86, 90
Montini, T., 83, 91, 373
Moog, F., 45
Moomaw, D.R., 137
Moon, H.P., 363
Moore, D., 308
Moore, F.D., 445
Moore, F.J., 187
Moore, H., 23
Moore, J.A., 48, 60, 61, 70
Moore, J.C., 160
Moore, J.T., 268
Moore, N.S., 193
Moore, P.T., 26
Moore, R., 401, 513
Moore, T.E., Jr., 184
Moore, W.W., 472
Moos, W.S., 306
Morales, M.F., 61, 63, 66, 124
Morczek, A., 306
Morehouse, M.G., 186
Morel, F., 93, 99
Morello, A., 264
Moreno, V.S., 468
Morgan, G.W., 278
Morgan, M.C., 183
Morgan, D.P., 154
Morgenthaler, H., 476
Morin, F., 405, 492, 494
Morin, G., 85
Morita, T.N., 140
Morpurgo, C., 451
Morrell, F., 504
Morrice, J.K.W., 503
Morris, G.L., 375
Morris, J. McL., 475, 476
Morris, L.E., 284
Morris, R., 348
Morrison, P.R., 84, 91, 373
Morrow, J.S., 135
Morse, D.P., 167
Morse, W.I., 449
Moruzzi, G., 406, 489, 493
Moscovitz, H.L., 281, 371
Moser, A., 472
Mosier, H.D., 402, 468
Moskalienko, Y.E., 264
Moss, E.M., 129
Mott, J.C., 155, 166, 284, 381, 383
Mottram, R. F., 256, 259
Motulsky, A.C., 231
Motzny, P.E., 559
Mouille, P., 372
Moulden, E.J., 301
Mount, L.E., 166
Moureau, P., 208
Mours-Laroche, M.F., 92
Moussiaschikova, S.S., 575
Mowbray, G.H., 433
Moxley, T.I., 533
Moyer, J.H., 519, 547
Moyle, J.M., 29
Muacchia, X.J., 91
Muchow, G.C., 235
Mücke, D., 306
Mudd, S., 133
Mudge, G.H., 14, 15, 28, 31, 520, 530, 532, 537, 539, 547
Mudrick, C., 233
Muehrcke, R.C., 514
Mueller, G.C., 133, 473
Mueller, J.F., 344
Mugrage, E.R., 67
Muir, R.M., 141
Muirhead-Thomson, R.C., 353
Mukherjee, K. L,. 101
Mukherjee, S.R., 241
Mulder, D.W., 501
Mülke, G., 380
Muller, A.F., 530, 532, 533, 534, 542
Müller, E., 88
Müller, H., 433
Muller, O., 383
Mullick, V., 22
Mullins, L.J., 25
Mun, A.M., 385
Munck, O., 262, 515
Munro, A.F., 385
Munro, H.N., 194
Munro, W.N., 194
Munson, P.L., 403, 439, 448, 449, 451, 469
Muntwyler, E., 532, 533, 535, 537
Murakami, K., 406
Murdaugh, H.V., Jr., 519
Murmanis, L., 47
Murphy, C.W., 444
Murphy, I.S., 208
Murphy, J.V., 500
Murphy, Q., 72
Murray, J.B., 367
Murray, J.E., 545
Murray, M., 211
Murray, R.W., 490
Murtadha, M., 239, 242, 245
Murtha, E.F., 135
Muschke, H.E., 471
Musseni, E., 123
Mustard, W.T., 85
Myant, N.B., 452
Myers, D.K., 135
Myers, R.E., 500
Myers, S.M., 367
Mylle, M., 515, 516, 525

N

Näätänen, E.K., 444
Nachmansohn, D., 17, 133
Nadell, J., 185
Naeye, R.L., 212
Nagareda, C.J., 315, 317, 318, 319
Nagareda, C.S., 310
Nagatsu, T., 127
Nagel, H., 329
Nahas, G.G., 86, 91, 99, 165, 235, 283
Naile, B., 135
Naito, M., 476
Nakamura, K., 125, 433
Nakao, H., 400, 494
Nakashima, M., 527
Nakashima, T., 124
Nakayama, T., 448
Nalbandov, A.V., 468, 470, 472
Namajuska, I., 127
Namin, P., 496
Nanao, S., 47
Nance, M.H., 217
Naoumov, S.F., 581
Naoumova, T.S., 569
Napolitano, L.A., 410
Naquet, R., 399, 494
Nardone, R.M., 91, 373
Nash, C.B., 165, 274
Nash, J., 346
Nashat, F.S., 91, 92, 154
Nashold, B.S., 493
Nass, C.A.G., 471
Nassonov, D.M., 558
Natelson, S., 166
Nathan, P.W., 492, 496, 503
Nathans, J.W., 176
Naumienko, A.L., 264
Nauta, W.J.H., 398,400, 403, 502
Navakatikyan, A.O., 274
Necheles, H., 179, 181, 189, 265
Necheles, T.F., 231
Nedeljkovic, R., 514, 515
Needham, A.E., 60, 361
Needham, D.M., 136
Needham, J., 348
Neely, R.A., 207
Neff, W.D., 432, 495
Neher, R., 541
Neidleman, S., 132
Neihof, R., 19
Neil, E., 91, 92, 153, 154
Neilands, J. B., 365
Neill, D. W., 179
Nelken, D., 207, 208
Nelson, A., 304
Nelson, D. H., 97, 439, 444, 445, 448, 453
Nelson, O. E., 46
Nelson, R. C., 73

Nelson, W. D., 132
Nelson, W. L., 476
Neptune, W. B., 85
Nesmeianova, T. N., 576
Netravesish, V., 245
Neufeld, H. A., 128
Neumann, W. F., 30
Neverre, G., 94, 101, 277, 407
Neverre, H., 90
Newcomer, W. S., 175
Newey, H., 185
Newlands, M. J., 209
Newman, E. V., 246, 285, 375
Newton, B. A., 137
Newton, M., 235, 236
Niazi, S. A., 88
Nicholls, D., 87
Nicholls, J., 20
Nichols, C. W., 442
Nichols, R. L., 178
Nickerson, J. L., 232, 233, 238
Nickerson, M., 166
Nicol, T., 472
Niden, A. H., 160, 268
Nielsen, B. S., see Schmidt-Nielsen, B.
Nielsen, H., 183
Nielsen, K. C., 93, 100, 520
Nielsen, M., 158, 160, 378
Nielsen, M. D., see Damgaard-Nielsen, M.
Nielson, N., 284
Niemann, P., 470
Nieuwkoop, P. D., 42, 50
Nieweg, H. O., 183
Niewiarowski, S., 208
Nigtevecht, G. V., 42
Nikolaeva, G. V., 575
Nilson, J. M., 218
Nilsson, A., 474
Nilsson, O., 472
Nisada, S., 124
Nisell, O. I., 167
Nishie, K., 25
Nissen, H. W., 500
Nitowsky, H. M., 192
Nitschke, A., 86, 92, 93
Nixon, D. A., 17, 475
Noall, M. W., 474
Noble, R. L., 246, 439
Noel, R., 101
Noell, W. K., 164
Nolan, J., 220
Nomof, N., 231, 232, 233
Norberg, B., 99
Nordenström, B., 188
Nordmann, J., 140
Nordmann, R., 140
Nordquist, L., 93
Norins, A. L., 152
Norkina, L. N., 571
Northen, H. T., 71
Northen, R. T., 71
Northman, M. H., 191
Northup, D. W., 178
Norvell, S. T., Jr., 181
Novikova, L. A., 562, 569
Nowell, P. C., 319, 320
Nukada, H., 140
Nunes, A., 383
Nusser, E., 281
Nutting, W. L., 364
Nuzhdin, N. I., 307
Nyboer, J., 520
Nye, S. W., 309
Nylin, G., 232, 238, 239, 383

O

Oag, R. K., 70, 73
Oakberg, E. F., 477
Oberhelman, H. A., Jr., 180
Oberholtzer, R. S. H., 275
Obersteg, J. I., 217
O'Brien, D., 166
O'Brien, J. G., 211
O'Brien, J. P., 308
O'Brien, J. R., 207, 209
Öbrink, K. J., 32
Ochoa, M., Jr., 233
Ochs, S., 276, 405, 495, 496
Ochwadt, B., 262
Ochwadt, B. K., 539
Oda, J. M., 235
Odeblad, E., 305
Odell, T. T., Jr., 319, 320
Odor, L. D., 472
Oeconomos, N., 545
Oeff, K., 239, 240
Oeri, J., 222
Oester, Y. T., 285
Ogata, H., 406
Ogden, E., 267, 270, 286
Oger, J., 102, 449
Ogle, W. S., 411
O'Halloran, J. A., 166
O'Hara, M., 98, 99
Ohkura, Y., 190
Ohler, E. A., 448, 449
Okada, M., 440
Okada, T. S., 48
Okajima, T., 402, 406
Okamato, C., 407
Okano, H., 42
Okita, J. T., 384
Okuda, K., 183
Oleksyshyn, N., 272, 383
Olesovsky, B., 91, 92
Olivecrona, H., 526
Oliver, J., 521, 524, 527
Olivereau, M., 92, 96, 347
Olling, C. C. J., 449
Olmstead J. M. D., 409
Olney, J. M., Jr., 241
Olsen, N. S., 502
Olsen, P., 99
Olson, R. A., 132
Olson, R. E., 122
Olszewski, J., 406, 493
Olwin, J. H., 208
Olzewski, J., 497
Omachi, A., 93
Omoto, C., 189
O'Neal, L. W., 452
O'Neill, E. J., 84
O'Nell, T., 307
Opitz, E., 92, 94
Oppenheimer, J. M., 48
Oppenheimer, M. J., 286
Orbach, J., 500
Orbelli, L. A., 584
Ord, M. G., 299, 300, 310
Ordynskij, S. I., 286
Ore, G. D., see Dalle Ore, G.
Oreshouk, 582
Orias, O., 472
Orloff, J., 521, 531, 533, 534, 535
Ormsby, A. A., 518
Orr, P. F., 476
Orr, P. R., 61, 70
Orrego, F., 430
Orrego, H., 183
Orser, W. B., 364
Ørskov, S. L., 22
Ortiz, E., 471
Ortiz-Galvan, A., 504
Ortmann, R., 475
Orto, L., 194
Osborn, J. J., 91
Osborne, N. W., 277
Oscarsson, O., 407, 491
Osono, S., 441
Östlund, E., 362, 368
Ostow, M., 502
Ostwald, W., 5, 6
O'Sullivan, R. B., 68
Otani, T., 497
Otey, M. C., 194
Otis, A. B., 155, 156, 166
Ottaviani, P., 208
Ottavioli, P., 85, 86
Ottoson, D., 19, 490, 504
Ottoson, J. O., 496
Oufland, J. M., 558
Oushakov, B. P., 558
Ouspevitch, M. A., 563
Outler, J. C., 475
Overbeck, W., 261
Overbeek, J. T., 19
Overman, R. R., 239
Overton, J., 47
Owen, C. A., Jr., 209, 211, 212, 231, 232
Owren, P. A., 209, 219, 220, 221
Ozawa, G., 133
Ozawa, T., 127
Ozer, F., 218

P

Paaby, H., 444
Pace, J. W., 502
Pace, N., 234
Pack, J. T., 183
Padua, F., 383
Paesi, F. J. A., 470, 471

Page, E., 372
Page, I. H., 152, 273, 274, 275, 409, 519
Page, J., 236
Page, L. B., 92, 99, 520, 547
Pagliari, M., 86
Pahigian, V., 71, 72
Paintal, A. S., 153, 245, 372
Pakesch, F., 206
Palay, S. L., 440, 450
Palazzo, F., 50
Palmer, J. F., 124
Palmer, L. W., 311
Palmhert, H. W., 332
Panasewicz, J., 208
Pannikar, N. K., 337, 344
Pansky, B., 243
Pantin, C. F. A., 329
Paoletti, G., 83, 91, 372, 373
Papez, J. W., 405, 493
Pappas, R., 375
Pappenheimer, J. R., 155, 156, 258, 262, 516, 517, 518
Pardo, E. G., 122
Parizek, J., 477
Park, C. R., 22
Park, O., 59, 60
Park, T., 59, 60
Parker, G., 43
Parker, R. F., 70, 89
Parkes, A. S., 64, 67, 88, 89, 472
Parkins, W. H., 86
Parlin, R. B., 14
Parlow, A. F., 403, 527
Parot, L. M., see Mercier-Parot, L.
Parr, W., 307, 315
Parry, G., 337
Parsons, R. J., 231, 233, 236, 237, 238, 239, 243
Parviainen, S., 476
Paschkis, K. E., 87, 452
Pascoe, J. E., 407
Paseyro, P., 208
Pask, E. A., 166
Pasquier, G. B., see Bilski-Pasquier, G.
Passaro, G., 210
Passeau, L., 314
Passouant, P., 399
Passouant-Fontaine, T., 399
Passow, H., 23
Pasteels, J., 42
Pataki, J., 283
Paterson, J. C. S., 186
Paton, W. D. M., 86, 164
Patron, C. R., see Rizo-Patrón, C.
Patt, H. M., 299, 300, 301, 304, 306, 308, 309, 310, 314
Patterson, G. C., 257, 258
Patterson, J. L.,Jr., 264
Patti, F. J., 307
Pattison, A. C., 189
Pattle, R. E., 166
Patton, H. D., 182, 401, 402
Patzelt, V., 471
Pauker-Warren, R., 469
Paul, M. H., 366
Paul, N. H., 285
Paul, W., 231, 233, 238, 239, 272
Paul, W. M., 475
Paulescu, F., 134
Pauling, L., 75
Paulos, P., 167
Paulssen, M. M. P., 207, 209
Pavlovic, V., 90, 91
Pavlovsky, A., 221, 222
Pawel, N. E., 166
Payne, H. W., 471
Payne, J. M., 477
Payne, N. M., 60, 62
Payne, R. W., 472
Pearce, J. F., 156
Pearce, J. W., 245
Pearce, M. L., 246
Pearson, C. M., 371
Pearson, F. G., 92
Pearson, O. H., 454, 526, 543
Pearson, W. N., 307
Pease, D. C., 513
Pederson, E., 286
Peel, A. A. F., 381
Peers, J. H., 309
Peeters, G., 133
Peimer, I. A., 568
Peimer, M. A., 575
Peiss, C. N., 61
Pelluet, D., 60, 343
Pembrey, M. S., 84
Pendlenton, G. B., 166
Penfield, W., 494, 499
Peng, M. T., 233
Penhos, J. C., 473, 475
Peniston, W. H., 167
Penna, M., 365, 370, 379
Penrod, K. E., 90
Peon, R. H., see Hernandez-Peon, R.
Pepper, M. C., 92
Pereira, S., 383
Perkins, J. F., Jr., 157
Perkins, W. J., 86
Perl, E. R., 432, 495
Perlick, E., 218
Pernow, B., 273
Perot, P. L., Jr., 162
Perry, M. M., 46
Perry, S. V., 68, 124, 136
Perry, W. F., 452
Perry, W. L. M., 408
Peruzzo, L., 100
Pessotti, R. L., 130
Peter, F., 434
Peters, H., 334
Peters, J. P., 194, 240, 245
Peters, K., 100
Peters, R. A., 138
Peters, R. M., 156
Peters, T., 47
Petersdorf, R. G., 242
Petersen, M. C., 500
Peterson, D. F., 134, 304
Peterson, L. H., 255-98; 275, 279, 280, 281
Peterson, O. S., Jr., 231
Petsche, H., 501
Pettengill, O., 346
Pettersson, H., 164
Petty, T., 153
Peyser, P., 96
Peyton, W. T., 411
Pfaffmann, C., 491
Pfeiffer, C. C., 128
Pflug, I. J., 70
Phear, E. A., 194
Phelps, A., 60
Philipson, L., 306
Phillips, A. H., 138
Phillips, C. G., 495
Phillips, C. W., 189, 265
Phillips, F. A., Jr., 260
Phillips, F. S., 63
Phillips, G. E., 208
Phillips, R., Jr., 85
Philpott, D., 366
Piatt, J., 51
Piaux, G., 475
Pichotka, J., 85, 87
Pick, A., 284, 369
Picken, L. E. R., 343
Pickford, G. E., 347, 469
Pickford, M., 402
Picón-Reategui, E., 233
Piel, C. F., 513
Pieper, G. R., 384
Pieragnoli, E., 206
Piercy, M., 499
Piéron, H., 60, 64
Pierpont, H. C., 85, 96
Pierre, R., 87, 97
Pierson, B. J., 132
Pihl, A., 301, 308
Pigon, A., 331
Piiper, J., 161, 259, 262, 268, 516
Pilgrim, R. L. C., 344, 362, 364
Piliero, S. J., 243, 244
Pincus, G., 439, 444, 475
Pincus, S., 376
Pines, K. L., 125
Pinkham, B., 527
Pinkston, J. O., 91
Pirani, C. L., 270, 514
Piro, S., 101
Pirolte, M., 303
Pirzio-Biroli, G., 231
Pisciotta, A. V., 210
Pitney, W. R., 133, 241
Pittman, J. A., 453
Pitt-Rivers, R., 132
Pitts, R. F., 529, 530, 531, 532, 533, 537, 538, 539, 543
Pitts, W. H., 496
Piva, G., 369
Plane, P., 100
Planta, P. van, 23
Plantin,, L.-O., 444

Platner, W. S., 92, 93, 366
Platts, M. M., 531, 533
Pletscher, A., 23, 503
Plitman, G. I., 208
Plotz, E. J., 476
Plough, I. C., 242
Plummer, A. J., 277, 401
Plzak, L., 244
Pocidalo, J. J., 100
Poggio, G. F., 493, 501
Polak, M., 184
Polge, C., 67, 477
Poli, A. de, 451, 468
Policard, A., 166
Polis, B. D., 93
Polissar, M. J., 13, 15, 61, 62, 70, 72, 74
Pollack, V. E., 514
Pollard, H. M., 180
Polley, E. H., 430
Pollock, L. J., 499
Polzer, K., 286
Ponder, E., 59, 71, 72
Ponder, R., 72
Pontes, J. F., 184
Pontius, R. G., 89
Pool, J. G., 211
Poole, J. C. F., 209
Popjak, G., 245
Popov, G. V., 559
Popovic, V., 84, 87, 89, 90, 91, 93, 96, 98, 100
Poppell, J. W., 153, 529, 530, 532, 533
Popper, H. L., 189, 265
Poppi, A., 378
Poppin, J. L., 400
Porembinska, H., 207
Poretti, G., 20
Porfido, F. A., 262, 515, 516
Porjé, I. G., 265, 280
Porro, A., 125
Porszasz, J., 277
Port, S., 238, 239
Porter, J. C., 404, 449
Porter, K. R., 523
Porter, R. W., 448, 449, 538
Portman, O. W., 234
Portmann, C., 434
Portmann, M., 434
Post, M., 124
Post, R. L., 22, 235, 236
Post, R. S., 246
Post, S., 474
Potter, G. D., 364
Potter, V. R., 137, 138
Potts, A. M., 216
Potts, W. T. W., 343, 351, 352
Poutasse, E. F., 262
Poutonnet, J. M. S., see Strumza-Poutonnet, J. M.
Povotskia, G. M., 238
Powell, T. P. S., 398, 493
Power, M. H., 232
Pozo, E. C. de, 122
Pradhan, S. N., 286
Prakash, R., 385
Prat, V., 520
Pratley, J. N., 16
Pratt, J. H., 191
Pratt, R. T. C., 499
Prec, K. T., 381
Preedy, J. R. K., 544
Prem, K. A., 476
Prentice, T. C., 238, 239, 241
Prescott, D. M., 15, 32
Precht, H., 59, 70, 73, 74, 75, 84, 85
Prerovsky, I., 260
Pribram, K. H., 500, 502
Pribam, K. H., 432
Pribram, H. B., 502
Price, H. L., 123, 238, 242, 272, 383, 376
Price, J. W., 69, 70, 74
Price, K. C., 160, 268, 384
Prichard, M. M. L., 440
Prien, E. L., 536
Prijma, G. Y., 276
Prinzmetal, M., 371
Prior, C., 86, 98, 102
Pritchard, J. A., 476, 520, 547
Pritchard, W. H., 233, 238
Proctor, D. W., 269
Proescher, F., 220
Proffitt, M. M., 189, 265
Prosser, C. L., 329, 353, 360
Prudden, J. F., 130
Pruitt, R. D., 381
Pruneyre, A., 100
Prunty, F. T. G., 439
Pscheidt, G. R., 138
Puech, P., 372
Pultz, A. J., 375
Punt, A., 83
Purdy, F. A., 366
Puri, B. R., 66
Purnima, R., 193
Purpura, D. P., 94, 494, 495
Purves, H. D., 441, 442
Pyrstowsky, H., 443
Pyzik, S. W., 499

Q

Quastel, J. H., 127, 141, 187
Quastler, H., 314
Quattlebaum, J. K., Jr., 183
Querido, A., 97, 456
Quick, A. J., 208, 218, 220
Quilliam, T. A., 490
Quilligan, E. J., 375, 383
Quinn, M., 93, 235

R

Raaflaub, J., 28
Raaschoy, F., 514
Rabbione, B., 86
Rabiner, S. F., 183
Raboch, J., 478
Radcliffe, R. W., 519
Radenac, J., 475
Radford, E. P., Jr., 156
Radike, A. W., 176
Radner, S., 286
Radwin, H. M., 432
Raffuci, F. L., 85, 192
Raffy, A., 347
Rahm, W. E., Jr., 433
Rahn, A., 157
Rahn, H., 151, 155, 157, 167
Rahn, O., 70, 73
Răihă, N., 17
Rajevski, B., 65
Rakita, L., 371
Rakoff, A. E., 475
Rall, J. E., 439, 454
Rall, W., 497
Ralli, E. P., 93, 96
Ralyte, L. G., see Giltaire-Ralyte, L.
Rambach, W. A., 307
Ramback, W. A., 137
Ramcharan, S., 242
Ramon y Cajal, S., 398, 504
Ramos, J. G., 166
Ramot, B., 212
Ramsay, A. G., 521
Ramsay, J. A., 30, 320, 334, 340, 341, 352
Ramsey, C. G., 182, 439
Ramsey, E. M., 475
Ramsey, G. H., 263
Ramsey, L. H., 475
Rand, M., 371
Randall, H. T., 153, 529, 530, 531, 532, 533, 538
Randall, J. E., 280
Randall, R. G., 306
Randall, R. V., 454
Ranke, O. F., 433
Ranney, R. E., 365
Ransmeier, R. E., 94
Ransom, V. R., 123, 140
Ransom, S. W., 85
Ranzi, S., 45, 52
Rapaport, E., 158, 161, 269
Raper, R., 342
Rapaport, S. I., 209, 219, 220, 221
Rappaport, R., Jr., 49
Rask, I., 524
Rasmussen, G. L., 428, 434
Rasmussen, H., 157
Raths, P., 218
Ratnoff, O. D., 212, 216, 476
Rattenbury, J. C., 50
Rauschkolb, E. W., 451, 541, 542
Ravello, J. J., 455
Raven, C. P., 51
Ravitch, M. M., 281, 371
Rawi, I. E., 194
Rawles, M. E., 49
Rawlinson, W. A., 72
Rawnsley, A. I., 433
Rawson, R. W., 47, 439
Ray, B. S., 454
Ray, G., 215

Raynaud, J., 154
Rayst, P., 303
Read, R. C., 231
Read, W. L., 283
Real, J. D., 372
Reardan, J. B., 545, 546
Reategui, E. P., see Picon-Reategui, E.
Reber, W. E., 90, 374
Record, B. R., 217
Reddy, W. J., 439, 449, 453
Redgate, F. S., 276, 400
Redmond, R. F., 166
Redo, S. F., 239, 240
Reed, C. E., 239, 383
Reed, C. S. H., 185
Reed, E. A., 372, 373
Rees, C. W., 131
Rees, G., 70
Reesinck, M. J., 362
Reeve, E. B., 232
Reeves, J. L., 520
Reeves, T. J., 375
Register, N. D., 100
Rehak, M. J., 384
Rehm, W. S., 16, 179
Reichel, H., 87
Reichenthal, J., 140
Reichlin, S., 452, 453, 454
Reichman, S., 89
Reid, D. E., 475
Reid, J. A., 384
Reid, L. C., 410
Reifenstein, E. C., 457
Reifenstein, R. W., 182
Reiher, K.,H., 473
Reilly, J., 122, 369
Reilly, W. A., 231, 238, 242
Reimann, E., 265
Reimann, F., 265
Reimer, E. E., 216
Reinberg, A., 21, 74, 93
Reineke, E. P., 457
Reiner, J. M., 71
Reinert, H., 408
Reinhardt, W. O., 245
Reinhold, M., 499
Reis, A., 282
Reisner, E. H., 183
Reiss, B. B., 193
Reiss, M., 96
Reiss, R. S., 457
Reissig, M., 208
Reitan, R. M., 499
Reiter, M., 124
Relman, A. S., 527, 529, 531, 532, 533, 538
Remington, J. W., 277, 376
Renault, H., 213, 219
Renier-Cornec, A., 408
Renkin, E. M., 270
Rennels, E. G., 526
Rennick, B. R., 155, 166
Rennie, D. W., 547
Renold, A. E., 439, 449, 453
Renzi, A. A., 439, 449, 541
Renzo, M., 86
Rérat, D., 364
Reubi, F., 286, 515
Reuter, H., 70
Reverberi, G., 50
Rey, P., 60
Reyer, R. W., 51
Reyes, E., 403
Reynell, P. C., 192, 241, 267
Reynolds, M., 234, 237
Reynolds, S. R. M., 475
Reynolds, T. B., 189
Rhodes, B. M., 306
Rhodin, J., 19
Ribaut, S., 515
Ribbands, C. R., 353
Ribeiro, L. P., 134
Ricci, G., 399
Ricci, P. D., 477
Rich, M., 183
Richard, S., 89, 101
Richards, A. G., 91
Richards, D. W., 377
Richards, J. B., 83, 449, 520
Richards, M. D., 219, 220
Richards, R. K., 129
Richards, T. G., 260, 265
Richards, V., 167, 268, 284
Richardson, D., 45
Richardson, F. L., 476
Richardson, K. C., 476
Richelme, H., 85, 91
Richmond, J., 84
Richter, D., 503
Richter, M. L., 129
Richterich-van Baerle, R., 535
Ricketts, H. T., 178
Rider, J. A., 181
Ridgeway, E. R., 127
Ridley, R. W., 383
Rieben, A., 281
Riecker, G., 265
Riedesel, M. L., 92
Riemenschneider, P. A., 310, 311
Rieser, P., 217
Rietsch, M. L., 84, 87, 91
Rigdon, R. H., 234
Riggs, T. R., 28
Rigler, S. P., 180, 181
Riker, W. F., Jr., 369
Riley, H. P., 309
Riley, J. A., 140
Riley, P. A., Jr., 547
Riley, R. L., 156
Rinaldi, F., 401, 493
Rinaldi, R., 371
Rindani, T. H., 306, 449
Rinehart, J. F., 440
Rinehart, R., 401
Rinehart, R. K., 273
Rinfret, A. P., 443, 444
Ringer, R. K., 284
Ringler, I., 476
Rioch, D. M., 403, 404, 406
Rioch, D. McK., 447, 467
Riondel, A. M., 444, 542
Ripplinger, J., 360, 361, 364
Ripstein, C. B., 92
Riss, W., 469
Ritchie, H. D., 189, 266
Ritchie, J. M., 274, 410
Ritenour, R., 84
Rivera, A. S., see Soto-Rivera, A.
Rivers, R. P., see Pitt-Rivers, R.
Rivin, A. U., 161
Rizo-Patrón, C., 235, 283
Roan, P. L., 319, 320
Robb, J. S., 366
Robbe, H., 236, 237
Robbins, E. D., 189
Robbins, J. C., 191
Roberts, A., 210
Roberts, J., 369
Roberts, K. E., 153, 529, 530, 531, 532, 533, 538
Roberts, R. B., 29
Roberts, S., 132, 404, 448, 468, 524
Robertson, H. E., 28
Robertson, J. D., 19, 28, 274, 330, 332, 333, 335, 342, 343, 345, 346, 407
Robertson, J. S., 22, 191
Robertson, W. van B., 96
Robey, M., 475
Robiner, I. S., 565
Robins, K. I., 208
Robinson, D. S., 209
Robinson, F., 500
Robinson, J. R., 352
Robison, B., 467, 470
Robson, J. M., 311
Robson, M. L., 310, 314
Roche, J., 132
Rock, J., 475
Rodbard, S., 91, 93, 159, 236, 277, 384
Roddie, I. C., 256, 259
Roddie, R. A., 258, 259
Rodesch, J., 304
Rodewald, G., 268
Rodin, E. A., 501
Rodnan, G. P., 233
Rodriguez, M. I., 369
Rodway, H. E., 475
Roeder, K. D., 410
Roels, H., 47
Roeske, R., 526
Roger, A., 493,501
Rohmer, F., 94
Roitbak, A. I., 561, 563, 564, 567, 569
Roka, L., 213
Rolinson, G. N., 137
Rollins, L. T., 503
Romanoff, E. B., 475
Romer, A. S., 346
Romijn, C., 84
Romney, S. L., 475
Rondell, P. A., 270, 272, 311
Ronniger, R., 280, 376

Rønnov-Jesson, V., 519, 545, 547
Roorbach, E. H., 156
Root, W. S., 166, 231, 232, 243
Ropes, M. W., 242
Rosa, L., 371
Roschina, N. A., 575
Rose, B., 523
Rose, D. J., 284
Rose, J. C., 160, 239, 262, 267, 268, 377, 383, 515, 516
Rose, J. E., 430
Rose, J. G., 431
Rose, W. C., 195
Rosemberg, E., 447, 452, 467
Rosen, S., 183
Rosenberg, A. J., 127, 305
Rosenberg, B., 404, 447, 450
Rosenberg, E., 403, 404
Rosenburg, N. W., 19
Rosenblith, W. A., 417, 425, 427, 429, 432
Rosenblum, C., 183, 306
Rosenburg, M. J., 239
Rosene, H. F., 16
Rosenfeld, G., 452
Rosenfeld, S., 403
Rosenman, R. H.,186, 272, 372
Rosensweig, J., 259
Rosenthal, D. L., 558
Rosenthal, M. C., 212
Rosenthal, R. L., 212
Rosenthal, S. M., 241, 242, 245
Rosenzweig, M. R., 427, 429, 493
Rosin, H., 370
Rosnagle, R. S., 542
Rosner, B. S., 432
Rosomoff, H. L., 94
Ross, D. N., 85, 86, 90
Ross, J. F., 238
Ross, R. S., 238
Ross, W. C. J., 132
Rossanda, M., 133
Rossi, G. F., 406, 493, 494, 499
Rossier, P. H., 151, 155
Rossiter, R. J., 87
Rosti, P., 207
Roth, F., 91
Roth, G. M., 261, 271
Roth, K., 221
Roth, R. F., 233
Rothballer, A. B., 441, 450
Rothe, C. F., 375
Rothe, G., 475
Rothlin, E., 100, 122, 262, 372, 379
Rothschild, M. A., 232, 239, 245
Rothschuh, K. E., 368
Rothstein, A., 16, 26
Rotta, A., 378
Rotter, W., 262
Rougeul, A., 399
Roughton, F. J., 166
Rougier, G., 284
Rovetta, P., 495
Rowe, G. G., 263, 380
Rowen, M., 306
Rowlands, S., 241, 285
Rowson, L. E., 474
Rowson, L. E. A., 475, 477
Roy, A. C., 477
Roy, B. B., 136, 369
Roy, S., 215
Roy, S. K., 477
Roy, S. N., 477
Royce, P. C., 451, 541
Rozee, K. R., 139
Rozhansky, M. A., 566
Rubbo, S. D., 132
Ruben, L. N., 51
Ruberti, R., 101
Rubini, M. E., 529, 530, 531, 533
Rubino, F., 132
Rubler, S., 286
Ruch, T. C., 406, 411
Rudhe, U., 234, 287
Rudler, J. C., 86
Rudnick, D., 45, 51
Rudnik, A. I., 561
Rudolph, G. G., 502
Ruebner, B., 194
Ruedi, L., 434
Ruef, J., 259
Ruffin, J. M., 185
Rugh, R., 304, 305
Ruhe, C. H. W., 88, 154
Rummel, W., 20
Rumsfeld, H.W.,404, 449,524
Runnstrom, J., 47, 50
Rushmer, R. F., 279, 376
Rusinov, V. S., 569
Ruska, H., 71, 73
Ruskin, A , 130
Ruskin, B., 130
Ruskin, H. D., 188
Russ, C., 189
Russek, H. I., 264
Russel, R., 93
Russell, D. S., 446, 457
Russell, F. E., 25
Russell, G. V., 406
Russell, J. A., 367
Russell, R. L., 366
Russell, R. S., see Scott-Russell, R.
Russell, R. W., 93
Russell, W. R., 495
Russfield, A. B., 442
Rusu, E., 369
Rusznyák, I., 166
Ruz, F., 166
Ryan, A. E., 181, 182
Ryan, H., 26
Ryan, J. M., 157
Ryan, M., 305
Ryd, H., 86
Ryser, F. A., 84
Rystle, S. P., 123
Ryvkin, J. M., 87
Rzyman, B. D., 100

S

Saathoff, J., 92, 94
Sabateev, V. B., 575
Sabiston, D. C., 90, 374
Sabiston, D. C., Jr., 90, 374
Sachs, L., 476
Sadoul, P., 157
Saeki, Y., 469
Saens, M. S., see Saint Saens, M.
Saffran, M., 404, 450, 468
Sager, R. H., 536
Saiki, H., 93, 236
Sailer, E., 453
Saint-Marc, J., 449
Saint-Saens, M., 409
Saito, S., 449, 451, 468,, 469
Sakata, Y. B., 235, 283
Sakhatchiev, A,, 307
Sakhoulina, D. T., 568
Sakiz, E., 471
Sala, S. J. M., 42
Salamon, G., 85
Saleeby, E. R., 311
Saleeby, R. G., 208
Salerno, P. R., 301
Salikova, M. V., 575
Salisbury, P. F., 281, 376
Salmoiraghi, G. C., 152, 275, 409
Salonikides, N., 268, 285
Salpeter, M. M., 284
Salvatore, F., 244
Salvidio, E., 208
Salzberg, A. M., 241
Samama, A., 219
Samama, E., 218
Samama, M., 219
Samet, P., 154
Sampson, J. J., 233, 244
Samter, M., 306
Samuel, P., 383
Samuels, L. T., 444
Sancetta, S. M., 263, 284
Sandberg, A. A., 444
Sanders, A. P., 186
Sanders, A. T., 185
Sanders, H. L., 529, 531, 538
Sanders, M., 219
Sando, T. de, 85
Sandstead, H. R., 175
Sanfilippo, G., 470
Sanger, C., 162
Sani, G., 471
Sapeika, N., 439
Sapin, S. O., 281, 371
Sapirstein, L. A., 267, 270, 286, 374, 375, 515, 522
Sapuppo, C., 208
Sarajas, H.S., 91
Sarnoff, S. J., 158, 376, 379, 380
Sartorius, O. W., 519, 545
Sarzana, G., 132
Sassine, A., 273

Sass-Kortsak, A., 245
Sato, M., 25, 490
Sato, T., 141, 471, 503
Satran, R., 533
Saumont, R., 86
Saunders, P. R., 125, 379
Savinovskaia, A. A., 574
Savitsky, J. P., 207, 316
Sawa, M., 400
Sawers, R. J., 212, 222
Sawyer, C. H., 467-88; 45, 403, 404, 467, 468, 470
Sawyer, M. K., 350
Sawyer, W. H., 349, 350, 469
Sayers, G., 449, 450, 451
Saxén, L., 42, 49
Scalabrino, R., 133
Scano, A., 166
Scarborough, H., 542
Scatchard, G., 14, 19
Schabel, F. M., Jr., 132
Schaberg, A., 384
Schachter, D., 513
Schacter, B., 137
Schaden, W., 210, 222
Schaefer, E. H., 219
Schaefer, K. E., 162, 503
Schaefer, V. J., 63
Schaeffer, G., 96
Schafer, E. P. S., see Sharpy-Schafer, E. P.
Schaff, G., 100, 102
Schaffhauser, E., 279
Schally, A. V., 404, 450, 468
Schapiro, H., 178, 182, 183
Schapiro, S., 403, 449
Scharrer, B., 441, 450
Scharrer, E., 441, 450
Schatten, W., 189
Schatzmann, H. J., 21, 23, 125
Schaumann, W., 91, 100, 241, 274, 410
Schechtman, A. M., 43, 44
Scheele, C. W., 11
Scheibel, A., 489, 493
Scheibel, M., 406, 489, 493
Scheifley, C. H., 187
Scher, A. M., 371
Scherbel, A. L., 527
Scherf, D., 91, 369, 370
Scherrer, H., 500
Schicks, E., 30
Schiessle, W., 91, 99
Schieve, J. F., 374, 517, 520
Schild, A., 286
Schiller, F., 490
Schilling, J. A., 155
Schilling, R. F., 183
Schimmler, W., 262, 264
Schjeide, O. A., 64
Schlang, H. A., 310
Schlesinger, H., 179
Schlieper, C., 329, 351
Schlig, B. B., 154
Schlögl, R., 19
Schmandt, W. P., 519, 545
Schmid, A., 286
Schmid, F., 102
Schmid, R., 130
Schmid, W., 101
Schmidt, C. F., 153
Schmidt, K. P., 59, 60
Schmidt, L., 262
Schmidt, R. P., 493
Schmidt, W. J. H., 86
Schmidt-Nielsen, B., 100
Schmier, J., 380, 384,
Schmitt, H., 43, 408
Schmitt, H. G., 434
Schmitt, O. H., 371
Schmutzler, R., 208
Schnaper, H. W., 239
Schneider, C. L., 207, 208
Schneider, E. M., 181
Schneider, J. A., 273, 401
Schneider, M., 94, 309, 313, 314, 318
Schneider, W., 478
Schneider, W. G., 471
Schnellbacher, F., 264
Schniederman, A., 239
Schoedel, W., 91, 92
Schoenborn, H. W., 60
Schoenhyder, F., 63
Schoffeniels, E., 27, 342
Schofield, B. M., 473
Scholander, P. F., 60, 61, 65, 66, 67
Scholer, J. F., 184
Scholtissek, C., 122
Schoolar, J. C., 239
Schopfer, W. H., 344
Schork, P. K., 207
Schorn, J., 265
Schotte, O. E., 51
Schottstaedt, W. W., 444
Schrader, F., 47
Schrank, A. R., 51
Schreiber, S. S., 238
Schreibmair, G., 71, 74
Schreiner, B., 283
Schreiner, G. E., 233, 238, 239
Schreiner, L. H., 400, 403, 404, 447, 467
Schrevel, J. de, 272
Schricker, J. A., 453
Schriefers, H., 473
Schroeder, H. R., 400
Schroeder, J., 258, 259
Schroeder, K. R., 152
Schroeder, W., 286
Schröer, H., 123
Schubert, G., 433
Schuck, E. A., 178
Schuck, J., 473
Schück, O., 516
Schuermeyer, E., 259, 262, 516
Schuhfried, F., 286
Schuknecht, H. F., 432, 491
Schulman, J., 232, 233
Schultz, A. L., 233
Schultz, F. H., 96
Schultz, R. C., 526
Schulz, A. R., 137
Schulze, H. F. A., 470
Schuman, H., 91
Schuster, A., 474
Schuster, S., 30
Schütt, L., 23
Schwalb, H., 131, 262
Schwartz, N. B., 443
Schwartz, R., 474
Schwartz, S., 130
Schwartz, W. B., 527, 529, 530, 531, 532, 533, 538
Schweinburg, F., 282
Schweitzer, A., 160, 269
Schweitzer, C. H., 23
Schwiebinger, G. W., 514
Scibetta, M. P., 267
Scott, D., 492
Scott, G. T., 29
Scott, H., 96
Scott, J. C., 372, 373
Scott, J. L., Jr., 87
Scott, J. W., 93
Scott, K., 231, 233, 238, 242
Scott, K. G., 233, 234
Scott, R. B., 472
Scott-Russell, R., 16
Scow, R. O., 454
Scriabine, A., 365, 379
Seager, L. D., 160
Sealander, J. A., Jr., 83, 84, 89
Seaman, A. J., 220
Sear, H., 232, 233
Searcy, R. L., 186
Seeman, A., 476
Seegers, W. H., 205, 207, 208, 209, 210, 211, 212, 214, 215, 216, 217, 218, 219
Seevers, M. H., 127, 139, 410
Segal, R., 134
Segal, S. J., 470
Segar, W. E., 547
Segundo, J. P., 399, 493, 499
Sehon, A. H., 523
Seifriz, W., 72
Sieja, A., 190
Seip, M., 244
Seitelberger, F., 468
Sekizawa, Y., 133
Seldin, D. W., 244
Selenkow, H. A., 132
Selker, R. G., 189
Selkurt, E. E., 31, 266
Sellers, A. L., 233, 524
Sellers, E. A., 89, 306
Selman, G. G., 46, 47
Selverstone, N. J., 156
Semet, J., 384
Sem-Jacobsen, C. W., 500
Semm, K., 476
Semple, R. E., 242
Senda, N., 70
Seneque, J., 85
Senger, I. F., 94
Senkevich, E. V., 563
Sergeev, B. F., 573

Serr, D. M., 476
Sessions, S. M., 175
Sethna, S. S., 166
Seusing, J., 286
Sevastianova, L. B., 576
Severinghaus, J. W., 92, 151, 156, 410
Sevitt, S., 71
Sevy, R. W., 448, 449
Shadaksharappa, K., 457
Shadle, O. W., 160, 237, 268, 377
Shafar, J., 183
Shafer, C. W., 85, 93
Shaffer, A. B., 383
Shafrir, E., 207, 216
Shaklee, A. B., 501
Shamarina, N. M., 576
Shamir, Z., 207
Shanes, A. M., 24, 25, 93, 528, 529
Shanks, R. G., 258
Shapiro, A. P., 244
Shapiro, B., 301, 308
Shapiro, J., 157
Shapiro, N. I., 307
Shappelle, E., 187
Share, L., 542
Shargorodsky, L. Y., 574
Sharitova, R. R., 559
Sharma, L. R., 66
Sharpey-Schafer, F. P., 160, 242
Shatkin, J., 240
Shaw, F. H., 14
Shaw, J., 21, 30, 320, 335, 336, 339, 340, 341, 342
Shaw, S. N., 490
Shaw, T. I., 22
Shay, H., 191
Sheatz, G., 399, 500
Shelesnyak, M. C., 475
Shelley, H., 503
Shen, S. C., 45, 71, 72, 243, 503
Shepard, R. B., 279
Shepard, R. H., 156
Sheperd, J. T., 285, 374
Shephard, R.J., 153, 165, 167
Shepherd, J. T., 15d, 256, 259, 374, 375
Sheppard, E., 217
Sheridan, J. T., 545
Sherlock, S., 189, 194
Sherman, J. K., 67
Sherrod, T. R., 380
Sherry, S., 210, 216, 217
Shettles, L. B., 67, 476
Shibata, H., 194
Shibusawa, K., 441, 449, 451, 468, 469
Shideman, F.E., 127, 131, 139
Shillingford, J., 383
Shimada, H., 406, 448
Shingleton, W. W., 185, 186
Shinowara, G. Y., 208
Shintani, S., 128
Shipley, E. G., 469
Shipley, R. A., 477
Shirky, L. E., 443
Shirley, H. V., Jr., 468
Shivanov, A. A., 584
Shock, N. W., 284, 383
Shoemaker, W. C., 187
Shoemaker, W. L., 190
Shoenberg, K., 402, 403
Shoenberger, J. G., 240
Shohl, J., 166, 167
Shore, P. A., 503
Shoustin, N. A., 578, 585
Shriber, W. J., 90
Shull, A. F., 70
Shulman, A., 128
Shuster, S., 525
Sicher, K., 305
Sick, L., 376, 425
Siebenmann, R. E., 527, 532
Siegel, A., 90, 125, 367, 374
Siegel, B. V., 132
Siegel, J. H., 442
Siegel, S. M., 70, 71, 74
Sieker, H. O., 58, 245, 246, 268, 275, 283, 286
Siems, M. V., 91, 373
Sierens, G., 133
Sigenaga, M., 73
Sigg, E., 276, 405, 496
Sights, R., 240
Silber, E. N., 383
Silén, L., 364
Silver, P. H. S., 499
Silver, S. L., 503
Silverman, A., 305
Silverman, D., 500
Silverman, M. S., 314
Silvette, H., 97
Simay-Kramar, M., 271
Simmonds, W. J., 185, 241
Simmons, B., 232, 234
Simmons, D. H., 157, 452
Simmons, E. L., 310, 311, 314
Simmons, M. R., 307
Simon, S., 14, 17
Simonnet, H., 475
Simons, A., 97
Simonson, E., 91, 371
Simpson, M. E., 243, 244, 470, 475
Simpson, R., 74
Simpson, S., 93
Simpson, S. A., 439, 541, 542
Sinclair, D. C., 489, 490
Sinelnikoff, E. J., 86
Singer, B., 541
Singer, K., 212
Singer, M., 51
Singer, R. B., 153, 166, 167
Singher, H. O., 477
Sinizyn, N. P., 263
Sinks, J., 469
Siperstein, E., 442
Siplet, H., 191
Sippel, T. O., 45, 385
Sircar, P., 236
Sirlin, J. L., 44, 474
Sirse, M., 131
Sise, H. S., 212
Sisson, G. M., 167
Siurala, M., 184
Sivertson, S. E., 156
Sizer, I. W., 135
Sizer, J. W., 60
Sjoerdsma, A., 122, 181, 187
Sjølin, K., 211
Sjöstrand, F. S., 19
Sjöstrand, T., 91, 160, 231, 232, 234, 235, 236, 237, 238, 243
Skeggs, H. R., 306
Skillern, P. G., 527
Skillicorn, S. A., 182
Skipper, H. E., 132, 135
Skramlik, E. v., 433
Skrer, N., 83
Slater, E. C., 136, 366
Slater, I. H., 128
Slater, R. A., see Alfin-Slater, R.
Slater, R. J., 245
Sloan, C. H., 166
Slocombe, A. G., 361
Sloper, J. C., 402, 457. 468
Slotte, K. F., 64, 75
Slotten, D. S., 180
Sloviter, H. A., 67, 68
Slusher, M. A., 448
Small, A. M., Jr., 433
Small, W. J., 271
Smith A. E. S., 43
Smith, A. U., 88, 89, 93, 471
Smith, A. V., 67
Smith, A. W. M., 183, 187
Smith, C. A., 166, 417, 418, 419, 420
Smith, C. H., 232, 233
Smith, C. L., 299
Smith, C. N., 154
Smith, D. E., 218
Smith, D. J., 91
Smith, D. L., 153, 159
Smith, D. W., 347
Smith, E. H., 185
Smith, F., 311
Smith, F. D., Jr., 384
Smith, G. W., 93
Smith, H. W., 329, 345, 346, 348, 513, 521, 522, 525, 526, 529, 533
Smith, I. D., see Darian Smith, I.
Smith, I. S., 73
Smith, J. A., 124
Smith, J. D., 521
Smith, J. O., 131
Smith, J. R., 160, 268, 365 384
Smith, K. F., see Fremont-Smith, K.
Smith, L. L., 166
Smith, L. W., 86

Smith, M. C., 492, 496
Smith, P. E., 443
Smith, R. E., 190
Smith, R. I., 353
Smith, T. C., 476
Smith, W. M., 410
Smith, W. W., 239, 271, 311
Smithberg, M., 49
Smull, N. W., 166
Smyth, J. D., 65
Smythe, C. McC., 364
Snell, F. M., 15
Snell, R. S., 472
Snider, G. L , 268, 283, 378
Sobel, H., 367, 403, 449
Söderberg, U., 502
Soderstrom, N., 190
Sofio, G. S., 161
Soiva, K., 476
Sokic, P., 84, 89
Sokoloff, B., 307
Sokoloff, L., 264
Soliman, F. A., 471
Sollman, T., 67
Sollner, K., 19
Solomon, A. K., 14, 22
Solomon, H. C., 400
Solomon, N., 86
Solomon, S., 536
Somers, F., 134
Sondergaard, E., 210
Sonn, H., 124
Sorkov, F. M., 560
Sorter, H., 181
Sós, J., 192
Soto-Rivera, A., 258
Soulairac, A., 469
Soulairac, M. L., 469
Soulier, J. P., 207, 212
Sousa, A. de, 265, 287
Souzkalskaia, I. P., 558
Spach, C., 89, 92
Spadolini, I., 368
Spaet, T. H., 211, 212, 219, 220
Spanner, D. C., 63
Spanner, R., 475
Spargo, B., 536
Sparrow, A. H., 309
Spatz, H., 441, 468
Spealman, C. R., 235, 236
Speer, R. J., 210
Spence, W. T., 406
Spencer, W. A., 127
Sperry, R. W., 495
Sperti, L., 497
Spiegel, E. A., 494
Spiegel, M., 43
Spiegelman, S., 343
Spinks, J. W. T., 214
Sprio, H. M., 181, 182
Spirtos, B. N., 404, 455, 468
Spoelstra, A. J. G., 87, 96
Spoor, A., 434
Sprague, J. M., 493, 496, 498
Spratt, N. T., Jr., 49
Spray, G. H., 192
Sprecher, D., 166
Sproston, N. G., 344
Spurling, C. L., 221
Spurr, G. B., 87, 88, 89, 91, 373
Squire, J. R., 240
Squire, M. C., 23
Stacy, R. W., 280, 281
Stadhouders, A. M., 51
Stadie, W. C., 132
Staehelin, M., 132
Stafford, A., 371
Stainton, R., 85, 93
Stamler, F. W., 475
Stamler, J., 545
Stamm, J. S., 399, 500, 502
Stämpfli, R., 25, 287
Stanbury, S. W., 28
Stange, H.-H., 471
Stapel, S., 95
Stapp, W. F., 208
Starr, I., 286, 375
Starzl, T. A., 377
Stauffer, H. M., 286
Stead, E. A., Jr., 234
Steadman, L. T., 92
Steblay, R., 62, 74
Steck, I. E., 443
Stedman, R. J., 526
Steenberg, R. W., 445
Stefanini, M., 207, 208
Stefanovic, M. P., 92, 93
Steggerda, F. R., 350
Stein, D. H., 276
Stein, E., 372
Stein, H. B., 208
Stein, S. N., 162
Steinbach, H. B., 14, 20, 343
Steinbeck, A. W., 233, 240
Steinberg, H., 188
Steinberg, I., 161
Steinberg, M. S., 51
Steiner, G., 66, 72, 73,
Steinhardt, J., 75
Steinmann, S., 284
Sleisenger, M. H., 188
Stella, G., 497
Stellar, S., 264
Stemler, F. W., 89
Stender, H. S., 307
Stenström, S., 19
Stéphan-Dubois, F., 51
Stephens, G. J., 359-96
Stephenson, W., 344, 345
Sterky, G., 99
Sterling, K., 231
Stern, G., 232, 233
Stern, P., 179, 187
Steur, M., 471
Stevens, A. R., Jr., 187, 243, 245
Stevens, C. E., 87, 452
Stevens, G. E., 87
Stevens, J. R., 399, 401, 501, 502
Stevenson, J. A. F., 402, 521
Stevenson, T. D., 181
Stewart, F. C., 29
Stewart, F. H. C., 526
Stewart, G., 272, 383
Stewart, G. H., 286
Stewart, P. A., 166
St. George, R. C. C., 64
St. George, S., 273, 372
Stickney, J. C., 234
Still, J. W., 286
Stirmann, J. A., 130
Stock, A., 95
Stocken, L. A., 299, 300, 310
Stoerk, H. C., 542
Stohlman, F., Jr., 316
Stolkowski, J., 21, 93
Stolte, L. A. M., 471
Stone, C. P., 98
Stone, L. S., 51
Stone, W., 238
Stone, W. E., 138
Stoner, R. D., 317
Storer, J. B., 89, 299, 300, 309, 315
Storey, C. F., 161
Stork, W. J., 161, 167
Stormont, R. T., 91
Storrie, U. M., 132
Storstein, O., 377
Stover, J. W., 519, 547
Stover, J. W., 519, 547
Strait, L. A., 502
Strakhov, A. E., 563
Stranack, F., 514, 546
Strange, P. H., 433, 495
Stratmann, C. J., 490
Straus, W., 524
Strauss, E. B., 504
Strauss, F., 474
Strecker, R. L., 84
Street, F., 96
Strickeland, A. G. R., 73
Strickland, K. P., 135
Stringer, I. D., 72
Ström, G., 164
Stromblad, B. C. R., 408
Strömblad, R., 175, 176, 408
Stroud, A. M., 306
Stroud, M. W., 3rd, 162
Strudwick, J. I., 456
Strumza, M. V., 90
Strumza-Poutonnet, J. M., 90
Struppler, A., 372, 381
Struppler, E., 372
Stucki, J. C., 475
Stucki, P., 281
Studer, A., 131
Stullken, D. W., 87
Stunkard, A. J., 193
Stupfel, M., 92, 101, 156, 410
Sturgis, S. H., 473
Sturkie, P. D., 284
Stutz, H., 365
Stux, M., 442, 455
Suc, J.-M., 515
Suden, C. T., see Tum Suden, C.
Sudin, T., 519, 520

Suehiro, M., 471
Sugihara, S., 492
Sulak, B., 471
Sulkowitch, H., 457
Sullivan, W. J., 537, 538
Sulman, F. G., 469, 475
Sumi, T., 432
Summerhayes, J. L. V., 379
Summers M. N., 306
Summers, V. K., 504
Summerskill, W. H., Jr., 194
Sumner, J. B., 134
Sunahara, F. A., 377
Sundberg, A. L, see Ingelman-Sundberg, A.
Sunderman, F. W., 87, 92
Sundin, J., 61
Suomalainen, P., 84, 92, 93, 98
Surtshin, A., 246, 519, 545, 547, 548
Sussman, M., 50
Sutcliffe, J. F., 28
Sutherland, D. A., 231
Sutherland, G. B., 125
Sutherland, V. C., 127
Sutton, S., 432, 491
Suvanto, I., 84
Svaetichin, G., 19
Svihla, A., 84, 236
Svihla, G., 218
Svorad, D., 94
Swain, G. G., 133
Swales, W. E., 59, 70
Swan, A. A. B., 274, 407
Swan, H., 91, 93
Swan, H. J. C., 161
Swank, R. L., 242
Swann, H. G., 515, 518
Swanson, M., 523, 536
Swanson, R. E., 522, 525, 528, 529
Sweet, A. Y., 536
Sweet, N. J., 185
Sweet, W. H., 85, 92, 93
Swell, L., 184
Swenseid, M. E., 183
Swift, M. N., 178, 312, 314, 315, 318
Swigart, R. A., 179
Swim, H. E., 89
Swingle, W. W., 403, 447, 527
Swinyard, C. A., 449
Sydnor, K. L., 403
Symington, T., 442
Symmes, D., 433, 501
Symonds, P., 215
Szábo, J., 565
Szabó, G., 166
Szalay, S., 519, 520, 545
Szara, S., 216
Szasz, T. S., 499
Szatmari, A., 496
Szego, C. M., 132, 473, 477
Szekely, E. G., 494
Szekeres, C., 90, 91
Szentagothai, J., 491
Szent-Györgyi, A., 68, 72
Szereday, Z., 576
Szilágyi, T., 266
Szücs, E., 257
Szy, S., 99

T

Tabuis, J., 207
Taeschler, M., 372, 379
Tager, J. M., 67
Taggart, J. V., 131
Tait, J. F., 439, 541, 542
Takacs, L., 547
Takamoto, K., 48
Takano, H., 475
Takaoka, T., 190
Takata, K., 41, 43
Takats, G. de, 409
Takaya, H., 48
Takeshi, A., 207, 216
Taketa, S., 312, 314
Taketa, S. T., 178, 314, 315, 318
Takeuchi, T., 472
Talbot, N. B., 457
Talbot, S. A., 286, 375
Talbott, J. H., 85, 99
Taliaferro, W. H., 319
Talso, P. J., 384
Tam, R. K., 60
Tambuscio, S., 402
Tamm, I., 523
Tamm, J., 284
Tanabe, Y., 469
Tanche, M., 86, 87, 90, 92, 94, 100
Tang, P. C., 406, 411
Tannenbaum, M., 244
Tanner, F. W., 74
Tansley, K., 491
Tanz, R. D., 125
Tapley, D. F., 133
Tartakovskaia, B. E., 238
Tartock, D. E., 208
Tarver, H., 245
Tasaki, I., 417-38; 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 490
Tasker, R. R., 186
Taubenhaus, M., 284
Taubman, F., 384
Tauc, L., 407
Taugener, R., 30
Taub, R., 361, 362
Tausche, F. G., 319, 320
Tawast, M., 184
Taylor, A. C., 67
Taylor, C. V., 63, 73
Taylor, D. W., 162
Taylor, H. L., 245
Taylor, I., 14
Taylor I. M., 93
Taylor, J. D., 129
Taylor, M. G., 286
Taylor, N. B. G., 246
Taylor, R. D., 273
Taylor, W. F., 307
Taylor, W. J., 265
Tedeschi, H., 28
Tedeschi, R. E., 368
Tegarden, L., 70
Teichmann, H., 49
Teillac, A., 154
Teitelbaum, M., 381
Teitelbaum, P., 402
Telfer, T. P., 190
Telkkä, A., 179
Temesvári, A., 381
Temperley, H. V. N., 502
ten Bosch, J. J. van der Werff, see Bosch, J. J. van der Werff ten
Ten Cate, J., 65, 70, 94, 362
Tenchov, G., 307
Teng, H. C., 244, 381
Tenney, S. M., 152, 154, 363 369
Teodosio, N., 360
Teorell, T., 19, 27, 544
Terres, G., 500
Terry, L. L., 181
Teruya, T., 406
Terzian, H., 101, 400, 502
Terzioglu, M., 218, 410
Terzuolo, C. A., 493
Teschan, P., 73
Tessmer, C., 303
Test, C. E., 178
Teuber, H. L., 502
Tew, J. T., 301
Teysseyre, J., 469
Thaler, H., 271
Tharp. C. P., 521
Thauer, R., 100
Thayer, S. A., 473
Thaysen, J. H., 176
Theilen, E. O., 90, 285, 366, 374, 378
Theiler, R. M., 409
Theobald, G. W., 237
Therriault, D. G., 219
Thibault, O., 98
Thimann, K. V., 439
Thode, H. G., 175
Thoennes, G., 65
Thomas, C. A., Jr., 529
Thomas, E. D., 243
Thomas, E. E., 182
Thomas, H. D., 375
Thomas, H. V., 194
Thomas, J. E., 191
Thomas, J. G., 286
Thomas, L. B., 473
Thomas, L. M., 405, 492, 494
Thomas, N., 89
Thomas, P. K., 490
Thomas, S., 525, 540, 547
Thomasson, B., 262
Thomlinson, R. H., 162
Thompson, C. R., 470
Thompson, D. D., 540, 544
Thompson, K. T., 272, 383

Thompson, P.O., 433
Thompson, R.H.S., 135
Thomson, J.F., 129, 139
Thomson, J.R., 132
Thomsen, K., 475
Thomson, R.C.M., see Muirhead-Thomson, R.C.
Thomson, W.S.T., 194
Thorn, G.W., 439, 449, 453, 457
Thorp, R.H., 371
Threlfall, C.J., 15
Thulin, C.-A., 431, 433
Thuranszky, K., 270
Thurlow, W.R., 430, 431
Thwing, E.J., 433
Tiedemann, H(einz), 45
Tiedemann, H(ildegard), 45
Tigay, E.L., 499
Tildon, J.T., 192
Tillmann, K., 23
Tillmans, V.C., 180
Tillotson, C., 478
Timiras, P., 452, 457
Timm, C., 433
Timmer, R.F., 442
Timmis, G.W., 182
Tipton, S.I., 72
Tobian, L., 261
Tobias, J.M., 19, 20, 490
Tobin, M., 375
Tocantins, L.M., 205, 219
Toch, P., 315, 317, 318, 319
Toeschler, M., 122
Tohá, J., 244
Toivonen, S., 42, 49
Tolman, R.A., 385
Tolpin, M., 91
Toman, J.E.P., 129
Tomashefski, J.F., 157
Tomizawa, K., 449, 468, 469
Tomlin, S.C., 213
Tonndorf, H., 423, 426
Tonutti, E., 471
Tonzig, S., 52
Topchieva, E.P., 575
Topliff, E.D., 167
Torin, S., 370
Tornvall, G., 188
Toro, I., 378
Torok, T., 90, 91
Toshima, T., 441
Toshio, H., 400
Tosteson, D.C., 22
Totsuka, G., 433
Tourniaire, A., 384
Tourpaev, T.M., 95
Towbin, E.J., 161, 177, 269, 410
Townes, P.L., 43
Tracktir, J., 180
Traeger, J., 527
Trapina, V.P., 558
Trautwein, W., 92
Travis, A.M., 496
Treherne, J.E., 30, 340, 342
Trethewie, E.R., 369
Triantaphyllopoulos, D.C., 220
Tribe, D.E., 193
Trinkaus, J.P., 43
Tripod, J., 257, 261
Trofimov, L.G., 568
Troll, W., 210, 216
Trolle, D., 473
Trounze, J.R., 177
Trout, E.C., 184
Trusler, G.A., 92
Trussell, M.H., 70
Tsao, M.U., 166
Tschirgi, R.D., 502
Tsuchiyama, T., 69
Tsumori, H., 183
Tsung-min, L., 186
Tuba, J., 476
Tuchman, H., 263, 380
Tuchmann-Duplessis, H., 404
Tucker, I.N., 233, 234
Tucker, W.T., 375
Tula, J., 191
Tullner, W.W., 453, 473
Tuluy, S., 90, 374
Tum Suden, C., 96
Tunturi, A.R., 431, 433, 495, 501
Turba, F., 122
Turchetti, G., 471
Turner, A.W., 60
Turner, C.W., 476
Turner, M., 101, 490
Turner, M.D., 189
Turner, M.M., 96
Turner, N., 101
Turner, R.S., 96
Turpin, J.E.H., 519
Tuttle, A.H., 521
Tveten, H., 377
Tybjaerg Hansen, A., 262, 515, 516
Tyler, E.T., 477
Tyler, E.R., 477
Tyler, F.H., 444
Tyor, M.P., 240
Tysinger, D.S., 373
Tysinger, D.S., Jr., 86, 91
Tzegelnitskaia, E.S., 559
Tzobkallo, G.I., 567, 574

U

Ubbens, D.R., 434
Uchiyama, H., 432
Udenfriend, S., 133
Ugaz, C., 285, 375
Uhde, G., 476
Ulfendahl, H., 32
Ulin, A.W., 187, 190
Ullrich, K.J., 30
Ulrich, F., 245
Umbreit, W.W., 131, 141
Undenfriend, S., 187
Underhill, B.M.L., 188
Ungar, F., 452
Ungar, G., 313
Ungar, I., 367
Unna, K.R., 496
Upton, A.C., 299, 300, 306
Uramoto, M., 46
Uramoto, T., 406
Urbani, M., 501
Ursini, M., 101
Urso, P., Jr., 312
Ussing, H.H., 27, 31, 350, 525
Usui, K., 400
Utida, S., 47
Uttley, A.M., 502
Uvnäs, B., 180, 260, 276
Uyeki, E., 301
Uzman, L.L., 242

V

Vague, J., 381
Vakaet, L., 47
Valcourt, A.J., 473
Valdivia, L., 518
Valenstein, E.S., 469
Valentin, H., 157, 159, 269
Valerio, I., 95
Vanamee, P., 153, 529, 530, 532, 533
Vanatta, J.C., 519
van Baerle, R.R., see Richterich-van Baerle, R.,
van Bekkum, D.W., see Bekkum, D.W. van
Van Breemen, V.L., 407, 526
van Breemen, V.L., see Breemen, V.L. van
van Buchem, F.S.P., see Buchem, F.S.P. van
Van Creveld, S., 207, 209, 211, 222
van de Kamer, J.H., see Kamer, J.H. van de
Vandenbrouke, J., 222
Van der Feer, Y., 285
Vanderhaeghe, F., 48
Vanderlaan, W.P., 132
van der Lee, S., see Lee, S. van der
Van der Pol, E.T., 209
Vandersmissem, L., 370
van der Werff ten Bosch, J.J., see Bosch, J.J. van der Werff ten
Van Dyke, D.C., 243, 244
van Dyke, H.B., see Dyke, H. B. van
Van Dyke, R.H., 43
Van Eyck, M., 433
van Gilse, H.A., see Gilse, H. A. van
van Halteren, P., 73, 74
van Harreveld, A., see Harreveld, A. van,
van Houten, J.C., see Houten, J.C. van
Van Itallie, T.B., 193
Van Lancker, J., 314

Van Liere, E. J., 178, 234
Van Loon, K., 522
van Middlesworth, L., see Middlesworth, L. van
van Planta, P., see Planta, P. van
Van Reen, R., 137
Van Slyke, D. D., 194
Vanstenhuyse, F. E., 185
Van Stone, J. M., 51
van Wagenen, G., see Wagenen, G. van
Varagic, V., 407
Varangot, J., 476
Varetto-Denoël, J., 304
Varga, M. E., 581
Vargas, J. J., see Jiménez-Vargas, J.
Vargas, L., 183
Vargiu, L., 134
Varnauskas, E., 262, 383
Varney, R. F., 449
Vars, H. M., 86
Vartiainen, I., 186
Vastola, E. F., 494
Vatzouro, E. G., 584
Vaughan, B. E., 234
Vaughn Williams, E. M., 368, 369, 374, 377
Vavala, D A., 163, 283
Vazifdar, J. P., 371
Veall, N., 231
Veder, H. A., 207, 211, 222
Veghelyi, P., 99
Veghelyi, P. V., 192
Vegni, L., 86, 98, 102
Veil, C., 408
Veith, I., 489, 504
Velardo, J. T., 472, 473
Velasques, T., 155
Vellisto, I., 476
Venner, A., 166
Venning, E. H., 246, 476, 541
Venrath, H., 157, 159, 269
Verbanck, M., 262
Verboom, E., 471
Verel, D., 232, 237, 271
Verloop, M. C., 271
Vernejoul, R. de, 85, 86, 88, 91
Vernier, V G., 399, 500
Vernon, J. A., 433
Verosky, M., 166
Verstraete, M., 212, 222
Verzár, F., 15, 96, 453
Verzeano, M., 494
Vescia, F. G., 384
Vesell, M., 449
Vetter, H., 175, 209, 232
Vicino, N., 132
Vidovic, V., 65, 89, 96, 98, 453
Vidt, D. G., 270, 374, 515, 522
Vieille-Cessay, C., 361
Vigneaud, V. du, 526
Villalobos, T. J., 96
Villarreal, R., 32, 180, 439
Vellee, C. A., 133
Vellela, G. G., 129, 134
Vilstrup, T., 420
Vimeux, J., 470
Vinagger, H., 209
Violette, F., 163
Viranuvatti, V., 231
Virno, H., 281
Virtue, R. W., 85, 374
Visscher, M. B., 359-96; 91 184, 238, 270, 384, 525, 528, 529
Vitale, A., 108
Vizioli, R., 399
Vlasin, Z., 87
Vogel, H., 301, 308
Vogt, M., 452, 544
Voisin, A., 96, 101
Volkova, M. N., 563
Volquartz, K., 63
Volwiler, W., 186, 245
Volzhin, N. S., 579
Vonau, N., 176
von Békésy G., see Békésy, G. von
von Bertalanffy, L., see Bertalanffy, L. von
von Brand, T., see Brand, T. von
von Bubnoff, M., see Bubnoff, M. von
von Euler, C., see Euler, C. von
von Euler, U. S., see Euler, U. S. von
von Foerster, H., see Foerster, H. von
von Gierke, E., see Gierke E. von
Von Kaulla, K. N., 208
Von Korff, R. W., 368
von Kugelen, B., see Kugelen, B. von
von Werz, R., see Werz, R. von
von Wittern, W. W., see Wittern, W. W. von
Voridis, E., 258
Vorontzov, D S., 562
Vosburg, L., 449
Vosburgh, G. J., 29, 522
Voskian, J., 544
Voskresenskaia, A. K., 579
Vouk, V. B., 95, 408
Vuylsteek, K., 269
Vysotsky, N. N., 581

W

Wada, H., 474
Waddell, W. R., 180
Waddington, C. H., 44, 46, 47, 51
Wade, E. G., 530, 531
Wade, O. L., 189, 266, 284, 378, 515, 524
Wadsworth, G. R., 233, 283
Waelsch, H., 45
Wagenen, G. van, 475
Wagner, G., 43
Wagner, H. N., Jr., 527
Wagner, R. H., 211, 219
Wahle, G. H., 208
Wahle, G H., Jr., 188
Wahlund, H , 241
Waidl, E., 473
Waite, J. H., 208, 473
Wakelin, R. W., 138
Wakerlin, G. E., 519
Wakim, K. G., 276
Walaas, E., 22
Walberg, F., 406
Walcott, W. W., 232
Waldenström, J., 187
Walder, D. N., 259
Walford, R. L., 209
Walker, A. E., 493, 501, 502
Walker, A. R. P., 237
Walker, B. Q., 84
Walker, B. S., 134, 536
Walker, D. G., 475
Walker, J. M , 368, 377
Walker, L., 179
Walker, W., 210, 213, 214
Wall, P. D., 496
Wallach, D. P., 457
Walser, M., 231, 233, 239, 244, 521
Walter, O., 208
Walter, W. G., see Grey Walter, W.
Walters, W., 61
Walther, A., 88
Waltner, C., 474
Wang, H., 237
Wang, R. I. H., 128, 129
Wang, S. C., 402
Wangensteen, O. H., 85, 192
Wanner, H., 63
Wapler, C., 86
Warbrick, J. G., 472
Ward, D. N., 526
Ward, W. D., 433
Wardell, H G., 311
Wardener, H. D. de, 515
Wardener, H. E. de, 242, 525, 526
Ware, A. G., 85, 210, 219
Wariovaara, V., 61
Waris, E., 380
Warner, E. D., 214
Warner, W. A., 502
Warren, J. V., 238
Warren, S., 124
Warren, S. L., 92, 96
Warren, W. R., 191
Warringa, M. G. P., 232
Wartelle, O., 207
Wartmann, W. B., 381
Warwick, R., 406, 497
Wasserman, F., 369
Wasserman, K., 242, 270, 271
Watanabe, H., 400

Watanabe, T., 400
Watanabe, Y., 70
Watanuki, S., 472
Waterhouse, C., 242
Watkinson, G., 180, 410
Watman, R. N., 192
Watson, C. W., 496
Watson, D. W., 70
Watson, G. M., 183
Watson, J S., 263
Watson, K. M., 62
Watson, L. S., 547
Watts, D. T., 282, 519, 520
Watts, R. W. E., 175
Waugh, D. F., 218
Waxenberg, S. E., 456
Way, E. L., 448
Weatherall, M., 23
Weaver, A. N., 515
Webb, C. S , 83
Webb, D. A., 335, 352
Webb, G. N., 383
Webb, J. L., 123, 373
Webb, L. J., 139
Webb, P. P., 89
Webb, R. C., Jr., 377
Webb, T. L., 125
Weber, A , 124
Weber, J. F., 131
Weber, W., 51
Webster, J. C., 433
Wechsler, R., 264
Wedd, A. M., 369
Weeks, J. R., 139, 140, 141
Wegelius, C. W., 85, 88, 99
Wegener, J., 495
Wégria, R., 154, 237, 246, 520, 524, 537, 539
Weidmann, H., 273
Weidmann, S., 92, 125, 385
Weigand, F. A., 242
Weijers, H. A., 185, 186
Weil, A. A., 501
Weinberg, S., 263
Weinberger, L. M., 458
Weinbren, K., 524
Weiner, R., 471
Weiner, R. S., 167
Weingarten, W , 264
Weinstein, A. B., 263, 380
Weinstein, S., 499
Weinstein, T. M., 231
Weir, D. R., 47
Weise, V. K., 451
Weiss, H. S., 284
Weiss, J. M., 384
Weiss, L., 132
Weiss, P. A., 51
Weissbach, H., 187
Weisz, K., 283
Weisz, P. B., 50
Welch, A. D., 121
Welden, F., 132
Wellbourn, R. B., 179
Weller, J. M., 547
Wells, G., 155
Wells, G. P., 333
Wells, J. A., 131
Wells, L. J., 443
Wells, M. H., 186
Welsh, J. H., 361, 362, 363
Welt, L. G., 242, 513, 525, 527
Wenckert, A., 218
Wendt, C. F., 86
Wener, J., 96
Wenger, R., 372
Weniger, J. P., 44
Wenner, J., 268
Wennesland, R., 231- 54; 231, 232, 233, 234, 238, 240
Went, I., 257
Wentz, W. B., 264
Werff ten Bosch, J. J. van der, see Bosch, J. J. van der Werff ten
Werkö, L., 262
Werman, R., 207
Werneman, H., 154, 164
Werner, G., 100, 101
Wersäll, J., 420, 472
Werz, R. von, 92
Weschke, H. G., 433
Wessler, S., 284
Wesson, L. G., Jr., 527,539
West, C. D., 454, 526, 527, 543
West, J. R., 526
West, T. C., 370, 409, 472
Westermann, E., 368
Westfall, B. A., 93, 366
Westman, A., 472, 473
Weston, R. E., 286, 525, 526, 537
Westphal, U., 473
Wettstein, A., 541
Wever, E. G., 417, 420, 424 425, 427, 433, 434
Wever, R., 259, 286
Weyl, P., 97
Weyl, R., 166
Wezler, K., 282
Whalen, W. J., 166
Whaler, B. C., 185, 186
Wheeler, G. P., 132, 135
Wheeler, H. O., 266, 515, 524
Whelan, R. F., 256, 257, 259
Whitaker, W., 241
Whitcomb, E. R., 286
White, A., 245
White, C., 526
White, C. S., 166
White, H. L., 246, 547
White, J. C., 85, 92, 93
White, J. M., 140
White, T. D., 179
White, W. E., 32, 231, 238
White, W. F., 311, 317
Whitehead, R W., 125
Whitehead, T. P., 490
Whitehorn, J. C., 456
Whitelaw, J , 469
Whitfield, I. C., 431
Whitlock, D. G., 495
Whitney, R. J., 236
Whitrock, R. M., 410
Whittam, R., 31, 536
Whittembury, M. G., 235
Whitten, W. K., 475
Whittenberger, J. L., 151, 159, 164
Whittenbury, G. M., 283
Whitteridge, D., 274, 407, 491, 492
Whitty, C. W. M., 399, 495
Wiberg, G. S., 191, 476
Wick, A. N., 22, 140
Widdas, W. F., 16, 17, 23, 475
Widdicombe, J. G., 381
Widmer, J., 284
Wied, D. de, 449
Wied, G. L., 473
Wiedeman, M. P., 272
Wiedemann, H. R., 85
Wiemer, F. K., 51
Wiermsa, C. A. G., 338
Wiesbader, H., 449
Wieser, S., 469
Wiesinger, K., 151
Wiesner, B. P., 474
Wiggers, C. J., 280
Wigglesworth, V. B., 59, 60, 61, 70, 71, 340, 342
Wikgren, B. J., 348
Wikler, N. S., 239
Wilber, G., 91
Wilbrandt, W., 16, 17, 22
Wild, F., 209
Wilde, C. E., Jr., 46, 49
Wilde, W. S., 13
Wildschut, A., 86
Wilens, S., 49
Wilhelmi, A. E., 469
Wilkins, R. W., 285
Wilks, S. S., 307
Willems, 100
Williams, B. S., 244
Williams, C. B., see Bolene-Williams, C.
Williams, D. T., 281
Williams E. M. V., see Vaughn Williams, E. M.
Williams, F., 313
Williams, F. L., 263, 379
Williams, H. H., 193
Williams, J. K., 533
Williams, L., 90
Williams, M. H., Jr., 157, 160, 161, 269
Williams, R., 232, 233
Williams, R. B., 304
Williams, R. H., 452, 453, 457
Williams, T. F., 527
Williams, W. J., 476
Williams, W. L , 183
Williamson, B. J., 536
Willier, B. H., 51
Willitts, B., 266
Willmer, E. N., 346

Willmer, M., 70
Wills, J., 27
Wills, J. H., 135
Wilson, B. J., 241
Wilson, I. B., 17, 133, 136
Wilson, J. S., 520, 547
Wilson, M., 123
Wilson, P. W., 60
Wilson, R. H., 166
Wilson, T. H., 138
Wilson, W. L., 47, 48
Winberg, H., 72
Winbury, M. M., 370, 372
Winderman, S., 372
Windesheim, J. H., 271
Windle, W. F., 504
Winfield, J. M., 242
Winitz, M., 194
Winnik, H. Z., 469
Winstone, N. E., 476
Winter, M., 96, 139
Winternitz, M., 369
Winters, R. W., 527
Winterstein, H., 92, 151, 152, 162, 334
Winton, F. R., 29, 513, 516
Wintrobe, M. M., 234
Wirtschafter, Z. T., 475
Wirz, E., 257, 261
Wise, B. L., 406, 545
Wislocki, G. B., 475
Wisner, A., 434
Witham, C., 372
Witschi, E., 49, 52
Witt, D. M., 447
Witt, I., 157, 268
Witt, P. N., 21, 125
Witt, W. T., 518
Witte, S., 210, 214
Wittern, W. W. von, 433
Wittkower, E. D., 456
Witzleb, E., 152, 275, 409
Woelsch, H., 129
Wolf, G., 172
Wolf, M. M., 263
Wolf, N. E., 272
Wolf, R. C., 477
Wolff, E., 44, 47
Wolff, H., 70
Wolff, H. G., 444
Wolff, J., 452, 454
Wolff, P. H., 502
Wolfson, S. K., 125
Wolfson, W. Q., 182
Wollenberger, A., 122, 124
Wolterink, L. F., 536
Wolverkamp, H. P., 61
Womersley, J. R., 286
Wong, S., 545
Wong, S. H., 443
Wood, C. D., 492, 496
Wood, E. H., 158, 161, 279, 285, 374, 375, 383
Wood, J. E., 258, 281
Wood, J. L., 135
Wood, J. S., 188
Wood, M. S., 457
Wood, P. A., 245
Wood, T. H., 65
Woodbury, D. M., 129, 457, 503
Woodbury, L. A., 92
Woodbury, R. A., 165, 274, 538
Woodbury, J. W., 69
Woods, J. W., 455
Woods, L. A., 139
Woodward, E. R., 178, 180, 182, 183
Woodward, G. E., 140
Woollam, D. H. M., 502
Worcester, J., 457
Worden, R. E., 281
Wort, D. J., 139
Worthington, W. C., 440
Wright, E. A., 308
Wright, I. S., 217
Wright, J. T., 183
Wright, L. D., 306
Wright, M. K., 500
Wright, M. R., 51
Wright, R. D., 176
Wroblewski, F., 380
Wu, M. L., 418, 420
Wulff, H. B., 86
Wulkan, E., 181
Wybourn, R. C., 313
Wyburn, G. M., 491
Wyckoff, R. W. G., 497
Wyers, E. J., 493
Wylie, D., 242
Wyngarden, L. J., 166
Wyss, O. A. M., 83, 409, 497
Wyss, V., 166
Wyssling, A. F., see Frey-Wyssling, A.

Y

Yakovlev, P. I., 400
Yall, I., 136
Yalow, R. S., 232, 233, 238, 239, 245
Yamada, H., 449, 468, 469
Yamada, T., 41, 43, 400
Yamamoto, H., 476
Yamamoto, S., 492
Yamasaki, H., 190
Yamasaki, S., 503
Yaoi, H., 306
Yardley, J. H., 188
Yates, F. E., 284
Yates, P. A., 525, 540, 547
Yntema, C. L., 49
Yokohama, T., 400
Yoshii, N., 407
Yoshimura, F., 451
You, S. S., 89
Youmans, J. R., 501
Youmans, W. B., 547
Young, A. C., 155, 167, 371
Young, C., 93, 236
Young, C. M., 193
Young, F. G., 132, 478
Young, H., 83
Young, I. E., 242, 377
Young, J. Z., 497
Young, M. K., Jr., 130
Young, W. C., 469
Yount, E. H., Jr., 262, 519
Yuceoglu, Y. Z., 373
Yudkin, J., 193, 474
Yuhara, M., 474
Yuile, C. L., 524
Yukihara, U., 400

Z

Zacks, S. I., 362
Zacouto, F., 86, 281
Zacutti, A., 471
Záhoř, Z., 477, 478
Zajic, F., 520
Zamfir, C., 369
Zamorano, B., 468
Zander, J., 473
Zarrow, I. G., 453
Zarrow, M. X., 453, 469, 471
Zatti, P., 497
Zayat, A. F., 385
Zbinden, G., 131
Zeavin, I., 91, 93
Zeller, E. A., 131
Zelter, E., 369
Zerahn, K., 27
Zerbino, V., 265
Zhukov, E. K., 559
Zieve, L., 179
Ziffren, S. E., 191
Zighera, C. F., 402
Zimdahl, W. T., 381
Zimmerman, W., 471
Zins, G. R., 134
Zinsser, H. H., 474
Zirmoonskaia, E. A., 560
Zirondoli, A., 493, 494
Zitrin, A., 405, 469
Zivin, I., 499
Zohman, B. L., 264
Zotterman, Y., 176, 491
Zsamar, E., 99
Zsigmond, E., 277
Zubchenkov, W. I., 286
Zucker, M. B., 208
Zuckerman, S., 187, 471, 474
Zuethen, B. W., 272
Zweifach, B. W., 272
Zwemer, R. L., 125
Zwilling, E., 49
Zwirn, P., 95
Zwislocki, J., 425, 427 433
Zygmuntowicz, A. S., 457
Zykina, E. S., 574
Zylka, W., 94

SUBJECT INDEX

A

Acetate, heart use of, 366, 379
Acetazoleamide, respiration and, 154
Acetylcholine
  cerebral transmission and, 503
  denervation sensitization to, 408
  heart action of, 95, 360, 361 364, 368, 369, 373, 374
  liver circulation and, 189
  peripheral circulation and, 257
  spinal inhibition by, 563
  splanchnic blood flow and, 266
  transmitter function of, 407, 408
Aconitine, heart fibrillation and, 369
Actomysin, heart muscle and, 365, 366
Adenine, heart and, 379
Adenohypophysis
  adrenal glands and, 439-58
  cell types in, 470
  culture of, 447, 450
  hormones of
    cellular origin of, 441, 422
    see specific hormone, e. g Adrenocorticotropic hormone
  hypophyseal portal system of, 440, 441, 446, 449-51
  hypothalamic control of, 439-41, 446-51, 457, 458
  isolation of, 446, 447
  reviews on, 439
  stalk section and, 446, 447
  thyrotropin secretion by, 404
Adenosine phosphates, heart and, 364-66, 379
Adrenal cortex
  adenohypophysis and, 439-58
  aldosterone, see Aldosterone
  ATP effects on, 381
  disease produced by, 439
  emotional stress and, 444
  hypothermia and, 97, 101, 102
  reviews on, 439
39 stalk section and, 446
  steroid hormones of
    placental transfer of, 443
    sites of action of, 543
    sympathicomimetic effects of, 543
  steroid hormones of, see also Aldosterone, Cortisone, etc.
  stomach secretion and, 179, 180, 181
  surgical trauma and, 444,. 445
  thyrotoxicosis and, 456, 457
Adrenal medulla
  hypothermia and, 96, 97, 101, 102
  peripheral circulation and, 277
Adrenocorticotropic hormone (ACTH)
  aldosterone secretion and, 451
  cellular origin of, 442, 443
  coronary flow and, 381
  limb regeneration and, 51
  reproduction and 468
  secretion of
    embryology of, 443, 444
    Graves' disease and, 457
    hypothalamus and, 403, 404
    neurohypophysis and, 450, 451
    neurosecretion and, 441
    portal transmitter for, 449-51
    pregnancy and, 443
    review of, 439
    stress and, 443-50
    thyrotropic hormone secretion and, 453
  stomach secretion and 179
  thyroid inhibition by, 452
Aldosterone
  clinical aldosteronism and, 452
  review on, 439
  secretion of, 451, 452, 542
Amino acids
  appetite and, 193-95
  blood patterns of, 193-95
  heart and, 364, 365, 367
  intestinal absorption of, 187
  physiological effects of, 186
  toxicity of, 193
Ammonium chloride
  chemoceptor stimulation by, 52
Amphibia
  embryology of, 43, 45
  skin permeability in, 349
  water-salt balance and endocrines in, 349-51
Amygdala, see Limbic system
Androgens, 477-78
  adrenal cortex and, 478
  muscle metabolism and, 478
Anemia
  blood volume and, 240-41
  radiation effects and, 314-15
  splanchnic blood flow in, 264
Anesthesia
  auditory mechanisms and, 432
  autonomic functions and, 407
  brain electrical activity and, 565
  cardiac output and, 383
  circulatory changes in, 165
  lung blood volume and, 160
  respiration and, 151, 156
  vagus stimulation and, 153
Anesthetics, local
  heart arrhythmias and, 370
Annelida
  ionic regulation in, 334
Anticholinesterase,
  heart and, 369
Anticoagulants
  coronary flow and, 380
Antidiuretic hormone, 526-27
  ACTH secretion and, 450, 451
  amphibians and, 350-51
Antihistaminic drugs
  heart arrhythmias and, 370
  skin blood flow and, 257
Anxiety
  pain perception and, 499
Appetite, 193-96
  hypothalamus and, 402, 403
  reviews of, 193
Arterial pressure
  cerebral cortex and, 405
  cold pressor test and, 261
  congestive heart failure and, 285
  coronary flow and, 263
  hypothermia and, 91, 101
  liver blood flow and, 266
  measurement of, 286
  pulse pressure and 278-81
  vasomotors substances and receptors, 274
  venous pressure and, 281
Arteries
  elasticity of, 278
  pulse wave in, 278-80
Arteriovenous anastomoses
  eye and, 270

intestine and, 270
kidney and, 262
liver and, 270
muscle and, 259
pulmonary circulation and, 268
skin and, 259
Arteriovenous fistulas
blood volume and, 237-38
diagnosis of, 161
Atropine
heart effects of, 360, 363, 364, 368, 369, 370, 379
peripheral circulation and, 256
respiratory dead space and, 156

B

BAL, heart function and, 365
Barostatic reflexes
afferent fibers of, 410
Basal ganglia
lesions of, 579
motor function and, 496
Benzoquinonium
heart and, 361, 362
Biliary system
ampullar resistance, 190
Bilirubin
plasma form of, 190
Bladder, urinary
bicarbonate exchange in, 539
micturition reflex, 406
nerve control of, 402, 411
receptors in, 410
sensations from, 574, 575
Blood
clotting of, see Coagulation, blood
fish blood composition, 346
gas content of, 166, 167
invertebrate blood composition, 342, 343
osmotic pressure of, 336-39
Blood flow
blood viscosity and, 260
measurement of, 256-61, 285-86
Blood platelets, 205-08
radiation and, 207, 315
serotonin and, 208
Blood substitutes
coronary flow and, 379
pulmonary blood flow and, 377
Blood volume, 231-46, 271, 272
Blood volume
altitude and, 234-35
cardiac insufficiency and, 238-39
disease and, 237-43
exercise and, 234
hematocrit and, 271
hepatic disease and, 239-40
hypothermia and, 91
measurement of, 161, 231-33, 271-72
normal values of, 233-34
plasma expanders and, 242
pregnancy and, 236-37
pressure breathing and, 165
pulmonary, 160, 161
receptors for, 243, 245, 275
regulation of, 231, 243-46, 281
hormones and, 246
kidney and, 246
nervous system and, 245
renal disease and, 239-40
responses to stress, 234-35
reviews of, 231
temperature and, 235-36
Bone marrow
radiation effects on, 304, 306, 307, 310-15
Brain
activity mapping in, 504
anesthesia and, 565
blood-brain barrier, 502
blood flow in, 264, 502
methods for, 264
electrical activity of explosive decompression and, 164
endocrine influences on, 503
humoral transmission in, 503
hypothermic death and, 88, 94
metabolism of, 125-29, 503, 504
chlorpromazine and, 100
glia cells and, 497
review of, 489
Ouchtomsky's dominanta, 564, 569, 577, 581
reproduction and, 467-71
sleep and, 566, 567
sympathetic effects in, 409
Brain stem
afferent systems in, 492, 493
auditory mechanisms, 430 431
sensory stimulation and, 564
visceral functions of, 406, 407
Butyrate, heart and, 366

C

Cadium, heart effects of, 372
Caffeine
heart metabolism and, 367
Calcium
heart action and, 372
hypothermia and, 92, 101, 373
invertebrate regulation of, 333, 345
Capillaries
circulation in, 269-71
filtration through, 165
heart muscle, 263
permeability of, 270-71
pressure in, 258
Carbon dioxide
brain excitability and, 503
breatholding and, 166
cerebral blood flow and, 264
chemoceptor stimulation by, 152
diffusion respiration and, 165
heart and, 369
oxygen poisoning and, 162
pulmonary exchange of, 155-57
pulmonary ventilation and, 153, 154
Carcinoids, 187
Cardiac output, 158, 374-76
age and, 383
anesthetics and, 383
arrhythmias and, 377
artificial respiration and, 164, 165
A-V shunts and, 375
ballistocardiography and, 375
drugs and, 382-84
exercise and, 378
heart metabolism and, 379
high altitude and, 378
hypothermia and, 90
measurement of, 374-76
patent ductus and, 166
pregnancy and, 383
respiratory cycle and, 374
Cell division, 47, 48
antimitotic agents, 48
drug action on, 132
Cells
cytochemistry, 64
cytoplasm of, 48
ice formation in, 67
nuclei of, 48
permeability of, 71, 331, 332
Cerebellum
activity of, 493
auditory effects in, 433
motor activity and, 496
Cerebral cortex
associative mechanisms of, 499-502
autonomic functions of, 405
chronaxie of, 405
conditioned reflexes and, 567-69, 574-78
efferent paths from, 495-97
electroencephalography, 500
emotion and, 398-400
epinephrine effect on, 405

frontal lobes of, 500
hearing and, 430-32, 495
hypothermia and, 94, 100, 101
inhibition in, 564
limbic system of, 398-400
see also Limbic System
localization in, 494-96
pain and, 494
peripheral circulation and, 261, 276
psychosomimetic drugs, 495
reticular formation and, 406
sleep and, 499
somatic sensory area of, 494, 495
spinal reflexes and, 562
spreading depression in, 500
thalamus and, 494, 496, 565
vision and, 495
Cerebrospinal fluid
brain nutrition and, 502
substance entry into, 28
Chemoceptors
peripheral circulation and, 275
respiratory control and, 409, 410
splanchnic nerve activity and, 266
Chloride
invertebrate regulation of, 335, 345
regulation in fish, 346
Chlorpromazine
reproduction and, 469
Cholesterol
liver handling of, 189
intestinal absorption of, 186, 192
Cholinesterase, 134, 135
embryonic heart and, 385
heart content of, 369
p-Choromercuribenzoate, heart and, 365
Circulation,
peripheral 255-87
blood viscosity,and, 282
critical closing pressure and, 260
extremities, 255-61
fetal, 475
methods, 285-87
nerve block and, 256
physiological stress and, 282-84
plethysmography for, 256-59
reflex regulation of, 273-78
splanchnic, 264-67
transmural pressures and, 257, 258, 260
vascular resistance and, 282
Coagulation, blood, 205-22
abnormalities of, 207, 209-13, 219, 221-22
antihemophilic factor, 211
antithrombins and, 217-18
antithromboplastins and, 207, 219
calcium and, 215, 216, 219, 220
cothromboplastic factors, 209-10
dicumarol and, 214
factor interactions in, 220-22
factor X and, 213
fibrinogen, 216-17
fibrinolysin and, 217
Hageman factor and, 212-13
hemophilia and, 211-22
heparin and, 218
K vitamins and, 214
plasma thromboplastin factors, 211-12
platelets in, 205-07
prothrombin and, 213-16
reviews of, 205
thrombin and, 216
thromboplastin and, 207-09
Cobalt
radiation protection and, 307
Cochlea
cochlear partition motion, 423-27, 429
electroanatomy of, 417-20
fluids in, 419, 420
microphonics of, 417, 420-27
steady potential in, 417-20
osmotic and ionic regulation in, 330-31
Cold
see Temperature, environmental
Colon
flora of, 188
motility of, 188
nervous control of, 410
Concussion, cerebral, reticular system and, 493
Congestive heart failure
see Heart, congestive failure of
Coronary circulation
see Heart, coronary circulation
Cortisone
adrenal inhibition by, 451
appetite and, 193
blood vessels and, 261
heart infarcts and, 381
iodine metabolism and, 452
pituitary inhibition by, 453, 456
stomach secretion and, 181, 182
thyroid inhibition by, 452, 456
Creatinephosphate, heart and, 364, 365
Crustacea
osmotic regulation in, 334-39
Curariform drugs
heart arrhythmias and, 369, 370
Cyanide
chemoceptor stimulation by, 152
heart action of, 364, 379
Cyclostomes
evolution of, 348
osmotic regulation in, 347-49
Cysteine, heart and, 365
Cytochromes, heart and, 366

D

DDT, heart and, 360
Decompression, explosive, 163, 164
Decompression sickness, 163, 164
Desoxycorticosterone, cell potassium and, 15, 27
Desoxyribonucleic acid
blood platelets and, 207
embryology and, 45
radiation effects and, 312-13, 318
Development, physiology of,
physiology of, 41, 52
antimetabolites and, 46, 47
books on, 51-52
cell affinities and, 43-45
cell migration and, 43-45
chemical differentiation and, 45
induction and, 41-43
invertebrate, 50-51
metabolism and, 45-46
proteins and, 44
special processes in, 47-48
vertebrate, 48-50
Dextran
blood volume and, 242
capillary permeability to, 270
Diabetes
glucose utilization and, 367
Dicumarol
blood coagulation and, 214
Digestion, 175-96
Digitalis drugs
calcium and, 369
cardiac output and, 382, 383
distribution of, 384
epinephrine and, 369, 379
heart action and 369, 371, 372, 378, 379, 384
heart metabolism and, 365, 366
metabolic inhibitors and, 379

potassium shifts and, 21
Diisopropylfluorophosphate,
heart and, 368
Dinitrophenol
embryology and, 45
heart and, 366, 379
Diphenylbutylamine derivatives
atrial fibrillation and, 370
Ditalen, heart pacemaker and, 360
Ductus arteriosus
closure of, 166

E

Ear
middle ear
biophysics, 417
function, 433
tympanic membrane, 417
see also Cochlea
Edema
heart disease and, 271
pulmonary, see Lungs, pulmonary edema
Embryology
see Development, physiology of
Emotion
adrenal secretion in, 444
cerebral cortex and, 398-400
conditioned reflexes and, 571, 572
endocrine histology and, 444
hypothalamus and, 502
psychosomatic mechanisms of, 504
stomach secretion and, 180
thyrotoxicosis and, 456
Emphysema, 153, 154
artificial respiration and, 164
work of breathing and, 165
Enteramine
see 5-hydroxytryptamine
Enzymes
cyanide and, 135
drug effects on, 133-41
heart metabolism and, 365-68
multiplicity of, 134
oxygen poisoning and, 162
temperature and, 61, 63, 69, 75
Epinephrine
autonomic ganglia and, 408
baroreceptors and, 274
calorgenic effect of, 96
cortical electrical activity and, 405
degradation of, 408
denervation sensitization to, 175, 176, 408
esophagus and, 178
heart action of, 263, 363, 369, 376, 377
ergotamine and, 368
exercise and, 378
hypothermia and, 373
heart failure and, 367
heart glycogen and, 367
heart pacemaker and, 360, 361
hypophyseal portal flow and, 440
hypothalamus activation by, 448
hypothermia and, 96, 97
insulin hypoglycemia and, 261
liver circulation and, 189
lung vasoconstriction and, 160
medullary function and, 563
muscle blood flow and, 256, 408
peripheral circulation and, 260
skin blood flow and, 256
splanchnic blood flow and, 265, 266
tactile receptors and, 408
vasomotor phenomena and, 256, 272, 273
see also Norepinephrine
Esophagus, 177, 178
motility of, 177, 178
pain from, 177
Estrogens, 472-73
renal effects of, 544
uterus and, 473
Ethylenediaminetetracetate,
heart action and, 372
Excretory organs
invertebrates, 334, 335, 337, 340, 341, 343
see also Kidney
Eye
chronaxy of, 561
extraocular muscles of, 95, 491, 492
intraocular fluid, 28
movements of
nervous control of, 497
nictitating membrane of, 409

F

Fat
intestinal absorption of, 185, 186
Fatty acids,
heart use of, 367
Fertility, 474-75
ovum and, 474-75
population control and, 474
sperm and, 474
Fertilization, 47
permeability changes in, 31
Fetal circulation, 381, 382
Fever
sensory factor in, 574
Fibrinogen
fibrinolysin and, 217
thrombin and, 216
Fish, ionic regulation in, 334-47
Fluoride
heart function and, 372
Freezing,
physiological effects of, 65-66

G

Gall bladder, 190
Ganglia
nerve cells in, 407
Ganglia,
autonomic
anesthesia and, 407
drug action on, 407
epinephrine and, 408
dorsal root
neurons of, 491
Geniculate body, lateral
potentials of, 494
Glial cells
metabolism of, 497
Glucose
appetite and, 193
blood content of
hypothalamus and, 402
hypothermia and, 95, 102
heart use of, 366, 367, 379
intestinal absorption of, 184, 185, 192
membrane transfer of, 16, 17, 22, 26
tolerance 178
Glutamic oxalacetic transaminase
myocardial infarction and, 380
Glutathione
radiation protection and, 303
Glutathionine
heart and, 365
Glycogen
content in heart, 366, 367
Gonadtropins
assay of, 471
cellular origin of, 441, 442
environmental factors and, 469
pituitary, 470
reproduction and, 467-71
secretion of
hypothalamus and, 404 458
urinary excretion of, 470, 471
Gonads
hypothalamic control of, 400
Growth hormone
aldosterone secretion and 452

H

Hearing, 417-35
acoustic trauma, 434
auditory nerve activity in, 417, 427-29
bone conduction, 433
central mechanisms of, 417, 430-32, 434, 495, 501
infraliminal stimulation in, 561
pitch discrimination, 425
psychophysics of, 433
sound localization, 493
see also Cochlea, Ear
Heart, 359-96
acetylcholine and, 95, 360, 361, 364, 368, 369, 373, 374
adenine nucleotides and 263
altitude adaptation and, 384
amines and, 364
anatomy of, 385
anticholinesterases and, 368
arrhythmias of
drugs and, 370
hypothermia and, 373. 374
atrial fibrillation
acetylcholines and, 368
anticholinesterases and, 368
atrial septal defects, 382
atropine and 360, 363, 364, 368-70, 379
benzoquinonium and, 361, 362
capillaries in, 263
cardiac reflexes, 372, 373
cardiac temponade and, 376
conduction time, 363
conducting tissue of
metabolism of, 367
congestive failure of, 382-83
actomyosin and, 365
blood volume and, 238-39, 272
extracellular fluid and, 239
diet and, 384
oxygen consumption in, 264
splanchnic blood flow in, 264
coronary circulation, 262, 263, 369, 376, 379-81
alcohol and, 380
anticoagulants and, 380
arrhythmias and, 377
hypothermia and, 90, 91
infarcts and, 380
shock and, 380, 381
sympathetic section and, 380, 381
decompression sickness and 163
diastolic volume law and, 376
digitalis drugs and 369, 371, 372, 378, 379, 384
electrocardiography
coronary flow and, 369
ion effects on, 371, 372
mechanical events and, 371
metabolic inhibitors and, 372
Q-T interval and rate, 372
temperature and, 373
uremia and, 369
vector analysis, 371, 372
electron microscopy of, 384
embryology of, 44, 385
epinephrine and, 263, 362, 363, 369, 376, 377
ergot alkaloids and, 362
extracts of, 361
fetal circulation, 381, 382
fetal conducting tissue of, 384, 385
fibrillation of
carbon dioxide and, 369
drug action on, 370
hypothermia and, 90, 93
myocardial infarction and, 370
potassium and, 369
glycogen synthesis
5-hydroxytryptamine and, 362, 363
hyperthyroidism and, 263
hypertrophy of, 378
hypothermic death and, 88, 89, 90
infarcts of, 381
inorganic phosphate in, 364, 365
ions and, 344, 345, 361, 372
insecticides and, 364
invertebrate, 344, 345
lesions of, 382, 383
load adaptation by, 376-79
metabolic inhibitors and, 364
metabolism of, 263, 364-68 379
diabetes and, 367
coronary flow and, 379, 380
drugs and, 367
hypothermia and, 374
infarcts and, 383, 384
mitochondria in, 366
mitral insufficiency
atrial pressures in, 157, 158
mitral stenosis
atrial pressures in, 157, 158
muscle of, see Muscle, cardiac
neural control of, 360-63
norepinephrine and, 263, 362
osmotic pressure and, 364
output of, see Cardiac output
pacemaker of, 359, 360, 370, 371
drugs and, 359, 360
intracellular potentials and, 359
invertebrate, 359-363
vagal stimulation and, 371
pentamethonium and, 362
pentobarbital effects on, 165
pH changes and, 369
phonocardiography, 384
phosphorylation in, 364, 365
physostigmine and, 362
pilocarpine and, 363
pulmonary edema and, 376
rate of
blood pressure and, 364
conditioning of, 576
contractile force and, 370
oxygen poisoning and, 162
oxygen tension and, 364
respiratory changes and, 373
temperature and, 89-92
receptors in
chemical stimulation of, 373
oxygen tension and, 372
refractory period of
drug effects on, 370
temperature and, 370
sodium transport in, 385
strychnine and, 362, 363
temperature changes and, 89-92, 373, 374
cardiac output and,374
coronary flow and, 374
ions and, 373
vagal stimulation and, 263
venous return and, 377
volume of, 376
working efficiency of, 263
Heat injury, 69-75
cell permeability and, 71
exposure time and, 70
resistance to, 73-74
reversibility of, 72
temperature coeficients of, 70
Helium
lung clearance of, 157
Hemoglobin
dissociation curve of, 166
Hemophilia, 211-13, 219, 221-22
Hemopoiesis
radiation effects and protection from, 303
recovery from, 310-20
Hemorrhage
blood volume and, 241-42
splanchnic blood flow and, 267
Heparin
antiheparin and, 207
blood coagulation and, 218

Heptaminol
heart failure and, 383
Hexamethonium
heart and, 368
lung vasoconstriction and, 160
Hibernation
see Temperature, body, hibernation
Hippocampus
see Cerebral cortex, limbic system
Histamine
liver storage of, 266
muscle action of, 179
peripheral circulation and, 257
splanchnic blood flow and, 266
stomach secretion and, 179
Hormones, behavior and, 469
behavior and, 469
blood volume and, 246
erythropoesis and, 243
mechanisms of action of, 132-33
oxygen poisoning and, 162
Hormones, steriod
review on, 439
Hunger, 193-96
Hydralazine
coronary flow and, 380
Hydrogen ion concentration
diffusion respiration and, 165
respiratory control and, 153-55
Hydroxybutyrate
heart use of, 379
Hydroxycorticosteriods
amygdala stimulation and, 400
hyperthyroidism and, 457
stress and, 444, 445
5-Hydroxytryptamine
see Serotonin
Hypertension
cerebral cortex and, 276
hormones and, 272
intracranial pressure and, 277
pulmonary, 268
sodium chloride and, 284
sympathetic nervous system and, 277
Hyperthermia
see Temperature, body, hypothermia
Hyperthyroidism
see Thyroid gland, hyperthyroidism
Hypophysis
see Pituitary gland, Adenohypophysis and neurohypophysis
Hypothalamus, 400-05
appetite and, 402, 403
blood sugar and, 402
conditioning and, 577, 578
emotions and, 502
gonadal function and, 400
gonadotropin release and, 404, 458
lesions of, 447, 449, 455
neurohypophysis and, 402, 403
obesity and, 402
olfaction and, 562
pancreatectomy and, 402
peripheral circulation and 276
pituitary regulation by, 439-441, 446-51, 457, 458
pulmonary edema and, 401
removal of, 447
reproduction and, 468
seizure inhibition from, 567
shivering and, 404
somnolence and, 404
stimulation of, 448
stomach erosions and, 182, 183
structure of, 401
taste and, 177
temperature regulation and, 95, 404, 502
thyroid activity and, 454-56
tranquilizers and, 401
tumors in, 468
urinary bladder and, 402
vascular anatomy of, 440
water intake and, 401-03
see also Temperature, body hyperthermia

I

Insecticides, heart and, 364
Insects, ionic regulation in, 339-42
Insulin
body temperature and, 86, 97
Intestine, large
see Colon
Intestine, small
absorption from, 184-87
length of, 188
motility of, 187, 188, 192
nervous control of, 406, 407, 410
mucosa of
peptic digestion of, 182
radiation effects on, 304, 312, 314, 315
transit time in, 192
Inulin properties and excretion of, 521
Invertebrates
ionic regulation in, 50, 51
Iodide
salivary content of, 175
Ionic regulation
active transport and, 351-54
comparative physiology of, 329-54
amphibia, 349-51
annelida and, 333-34
coelenterates and, 331-33
crustacea and, 334-39
cyclostomes, 347-49
fish and, 345-47
insects and, 339-42
methods in, 330
molluscs and, 342-44
nematodes and, 344-45
reviews of, 329
tunicates and, 345
genetic variations in, 353
Ions
active transport of, 351-54
heart effects of, 372
heat resistance and, 74
temperature and, 373
Iron, dietary
myocardial fibrosis and, 384
Insulin
appetite and, 193

K

Kidney
acid excretion, 532-33, 535 540
aciduria, paradoxical, 532
ammonium transfer by, 533-35
anatomy of, 513-14
anion excretion, 536-541
bicarbonate exchange, 537 537-39
biopsy of, 514
blood flow in, 261, 262, 514-21
arterivenous shunts and, 516
auto-regulation of, 516, 518
circulatory control of, 546-48
distribution of, 516
effects of drugs on, 262
extracellular fluid and, 519
hematocrit and, 261-62 518
glomerular filtration and, 546
hypothermia and, 520
measurement of, 262, 514-15
neural effects and, 518
occlusion of, 526
plasma skimming, 517
posture and, 520
pregnancy and, 520
pressure gradients in, 515
regulation of, 516, 518-21 546-48

reserpine and, 521
shock and, 520
vascular resistances in, 516
vasodilators and, 521
venous pressure and, 262
viscosity and, 517
calcium exchange, 535-36
chloride exchange, 536-39
citrate excretion by, 536
clearance
diodrast, 514
PAH, 515
concretions in 536
cyclostome, 348
denervation effects, 519
electrolyte excretion, 527-48
aldosterone and, 541-42
brainstem injury and, 545
cation transfer, 528-36
diurnal rhythyms in, 544
humoral control of, 541-44
hydrogen ion transfer and, 532
ion exchange and, 528, 531
nephron, isolated, 528
neural control of, 544-45
postural effects on, 547
radioautographs of, 528
regulation of, 541-48
embryology of, 43, 49
function of
adrenal medula and, 543
carbon dioxide and, 538
carbonic anhydrase and, 533, 539
conditioning of, 576
diabetes insipidus and, 526
glutaminase and, 535
hypothermia and, 99
invertebrates and, 29-31
nephron population shifts and, 547
glomerular filtration, 521-25
adrenalectomy and, 542, 543
diffusion and, 29
exercise and, 547
glucose load and, 525
hemorrhage and, 546
hypothermia and, 546
mechanism of, 522
methodology of, 521
nephron size and, 521
permeability and, 523
postural effects on, 547
unilateral anuria and, 548
heavy metal excretion by, 536
hemopoiesis and, 311
homotransplantation of, 545
homotransplantation of, 545
hydrogen ion transfer, 532-33, 535
interstitial volume of, 518
juxtaglomerular apparatus, 543
krypton, uptake of, 515
magnesium exchange, 535-36
metabolism of, 130, 131
neural regulation of, 544-46
osmoregulation by, 525
denervation effects, 545
load balance effects, 526
potassium deficit and, 527
transplantation and, 545
mercurial diuretics and, 526
para-amino hippurate transport in, 131
phosphate exchange, 539-40
potassium exchanges in 31, 527, 530-32
cation deple ions and, 531
mercurial diuretic effects, 530
mitochondria and, 530
tubular secretion and, 531
proteinuria, 523-24
sodium exchange in, 528-30
bicarbonate and, 530
carrier systems for, 529
denervation effects on, 545
potassium effects on, 529
sulfate exchange, 540, 541
teleost fish, 345
transplantation of, 515
water exchange, 525

L

Lactation, 476
hormones and, 476
nervous control of, 409, 476
Learning
body temperature and, 94
Leucocytes
potassium exchanges in, 24
radiation effects on, 306, 310
Limbic system
connections of, 501
excitability of, 501
motor functions of, 496
reflex activity and, 502
Lipides, heart failure and, 384
Lithium
heart effects of, 372
invertebrate embryology and, 50
Liver
appetite and, 195, 196
bromsulfalein and, 189
circulation in, 188, 189, 256, 264-267
cirrhosis of, 188, 189
excretion by, 189, 190
lymphatics of, 189
metabolism of, 129, 130
mitochondria of, 190
radiation effects and, 304, 318
vascular anatomy of, 256, 266
wedge pressures in, 265
Lobeline
chemoceptor stimulation and, 252
Lungs
alveolar-arterial exchange in, 157
artificial respiration and, 164, 165
atelectasis
gas exchange and, 155
blood volume in, 160, 161
bronchoconstriction in, 156
bronchoscopy of, 157
circulation in, see Lungs, pulmonary circulation
congestion of
Valsalva maneuver and, 161
decompression sickness and, 163
distensibility of, 165, 166, 382
edema of, 166, 376, 401
elasticity of, 165, 166, 382
emboli in, 160
emphysema, see Emphysema
explosive decompression and, 163, 164
fibrosis of, 165
gas exchange in, 155-161
atelectasis and, 155
A-V shunts and, 155
pneumoconiosis and, 156
high oxygen pressure and, 161-163
intrapleural pressure and, 269
nonuniform ventilation of, 156
poliomyelitis and, 153, 154
pulmonary circulation, 155, 157-161, 267-269
artificial respiration and, 164
blood volume in, 160, 161
catechol amines and, 377
collaterals in, 161, 269
drugs and, 159, 160
emboli in, 160
fetal, 382
hypoxia and, 159
intrathoracic pressure and, 159
mitral stenosis and, 157, 158
oxygen tension and, 158, 159
patent ductus and, 155
pericardial restraint and, 158
posture and, 159
pulsatile flow in, 158
reflexes and, 159, 160
right ventricle and, 267
sympathetic activity and,

268
systemic resistance and, 158
Valsalva maneuver and, 160, 161
vascular resistance in, 158, 159, 382
vasomotor activity in, 159, 160, 268
wedge pressures in, 158
pulmonary edema, 166, 376
hypothalamus and, 401
receptors in, 152, 153
volume of, 165
Lymph, 269-71
fat transport in, 185, 186
liver lymph, 189, 190

M

Magnesium
heart action and, 372
hypothermia and, 86, 92, 101
invertebrate regulation of, 335, 336, 345
membrane potassium and, 16
radiation protection and, 308
Mammary gland
hormones and, 476
Medulla oblongata
peripheral circulation and, 275
Membranes, biological
artificial models of, 19
microstructure of, 19
potentials across, 17-23
transport through, 13-32
Menstrual cycle
stomach secretion and, 180
Meperidine
circulatory adjustments and, 164
Mercurial diuretics
chloride transfer and, 537
phophorylation effects of, 530
potassium depletion and, 537
sites of action of, 537-38
Mesencephalon
peripheral circulation and, 276
Metabolic rate
embryonic development and, 45
exercise and, 378
hypothermia and, 86-88, 100
respiration and, 154
specific dynamic action, 87
vitamins, oxygen debt and, 378
Metabolism of microorganisms, 131-32
Metabolism, tissue
barbiturates and, 137
convulsant drugs and, 127, 128
dinitrophenol and, 137
fluoroacetate and, 137-39
fluorocitrate and, 138-39
metabolic pumps, 13, 15, 16, 29
pharmacological aspects of, 121-50
temperature and, 88
Methionine
heart and, 365
Methoxamine
heart fibrillation and, 370
Methylene blue
oxygen poisoning and, 162
Mitochondria
cell content of, 190
heart and, 366
lactation and, 476
potassium in, 15
swelling of, 28
Mitosis
radiation effects and, 304
Molluscs
ionic regulation in, 342-44
Monoiodoacetate
heart and, 365
Mucin
protective functions of, 182
Muscle,
cardiac
contractile proteins from, 124
glycoside effects on, 122 125
high energy phosphate in, 122, 124
ion fluxes in, 21
metabolism of, 123, 124
phophocreatine in, 124
temperature and, 92
skeletal
calcium flux in, 21
blood flow in, 256, 260
degeneration effects on, 559
epinephrine and, 408
freezing of, 66
glucose transfer into, 17, 22
heat rigor and, 72
potassium flux in, 14, 15, 18, 20, 21
sodium flux in, 14, 18, 20, 21
central control of spindles in, 489
tonic contraction of, 559, 560
Muscular exercise
appetite and, 193
Myotolon, see Benzoquinonium

N

Nematodes
ionic regulation in, 344
physiology of, 345
Neostigmine
heart and, 368
Nerve
chronaxy of, 558, 559
cold effects on, 95
conduction block in, 557, 558
excitability of, 557-60
gamma efferent system
cerebellum and, 496
mesencephalon and, 496
membrane potentials in, 17, 20
oxygen poisoning and, 162
parabiosis in, 557, 558
permeability changes in, 17
potassium flux in, 13, 14, 17, 20, 25, 26
sheath of, 24
sodium flux in, 24-26
Nerve cells
potentials of, 407
Nerve fibers
degeneration of, 490
Schwann cells and, 490
size of, 490, 491
unmedullated, 397, 398
Nerves
auditory
efferent fibers in, 434
electrical activity of, 417, 427-29
laryngeal
respiration and, 153
olfactory
nerve fibers in, 397
phrenic
stomach motility and, 179
vagus
bronchoconstriction and, 156
cardiac reflexes and, 371, 372
heart receptor fibers in, 381
intestinal motility and, 410
motor nucleus of, 406
stomach motility and, 178
stomach secretion and, 180
stretch receptors and, 153
Nervous system
regeneration in, 51
Russian neurophysiology, 557-85
somatic functions of, 489-04
visceral functions of, 397-411
Nervous system, central
metabolism of, 126-29
nerve fibers in, 398, 400
peripheral circulation and, 275-76
sensory perception and, 489
Neuroembryology, 49

Neuroendocrinology
reproduction and, 467-71
Neurohypophysis
ACTH secretion and, 450, 451
antidiuretic hormone of, see Antidiuretic hormone
conditioned secretion of, 576
hormones of
review of, 439
hypothalamus and, 402, 403
neurosecretion by, 441
stress responses and, 403
Neurosecretion
pituitary control and, 441
review on, 439
Nitrogen
lung clearance of, 157
narcosis and, 164
Norepinephrine
baroreceptors and, 274
heart failure and, 367
heart function and, 263, 362, 368, 369, 376, 377
heart glycogen and, 367
lung vasoconstriction and, 159, 160
muscle blood flow and, 256, 260
peripheral circulation and, 260
skin blood flow and, 256
splanchnic blood flow and, 265, 266
vasomotor phenomena and, 272
see also Epinephrine

O

Obesity
hypothalamus and, 402
review of, 193
Oleate
heart function and, 372
Osmotic regulation
comparative physiology of, 329-54
amphibia and, 349-51
annelida and, 333-34
coelenterates and, 331-33
crustacea and, 334-39
cyclostomes and, 347-49
fish and, 345-47
insects and, 339-42
methods in, 330
molluscs and, 342-44
nematodes and, 344-45
protozoa and, 330-31
reviews of, 329
tunicates and, 345
genetic variations in, 353
Ovulation
blockage of, 468-69
drugs and, 469
hormones and, 469
Ovum
fertilization and, 474-75
human, 475
Oxygen
artificial respiration and, 164, 165
blood content measurement, 166, 287
closure of ductus and, 166
diffusion respiration and, 165
high pressures of, 161-63
pulmonary exchange of, 155-57
toxicity of, 161-63
Oxygen deficiency
bile flow and, 190
cochlear potentials and, 419, 423
chemoceptor stimulation and, 152
hypothermia from, 85
pulmonary circulation and, 159
resistance to, 89, 102
respiratory control and, 153, 154, 409
Oxytocin
neurosecretion of, 468

P

Pain
central mechanism of, 494
conditioned reflexes and, 571
esophagus and, 177
nervous mechanisms for, 490, 499
neurosecretion and, 441
peptic ulcer and, 183
trigeminal neuralgia, 492
Pancreas
development of, 49
disorders of, 192
enzymes of, 191
hypothermia and, 97, 98
secretion of, 191, 192
Parasympathetic nervous system
colon and, 188
hypothalamus and, 401
Parathyroid glands
digestive system and, 183
Parathyroid hormone
renal effects of, 544
Pentamethonium
heart and, 362
Perception
brain function in, 499
Phosphate
heart muscle, content of, 364, 365
hypothermia and, 93
Phosphokinase
vasoactive drugs and, 384
Physostigmine
heart and, 362, 368
Pilocarpine
heart and, 363
Pitressin
ACTH secretion and, 451
Pituitary, anterior, see Adenohypophysis
Pituitary gland
aldosterone secretion and, 542
culture of, 447
hypothermia and, 98, 102
osmoregulation and, 347, 349-51
portal circulation of, 400
reproduction and, 467-71
stalk section and, 446
transplantation of, 447, 451
Pituitary, posterior, see Neurohypophysis
Placenta
ACTH secretion by, 443
ACTH transfer across, 443
adrenal steroid transfer across, 443
blood flow in, 475
hormones and, 475
morphology of, 475
sugar transfer through, 17
Plasma
calcium fraction of, 536
radiation protection and, 306
volume of
congestive heart failure and, 239
expanders and, 242
regulation of, 244
renal disease and, 240
Plasma proteins
myocardial infarction and, 380, 381
Poliomyelitis
artificial respiration and, 164
Polycythemia
blood volume and, 240-41
Potassium
acetylcholine liberation and, 408
aldosterone secretion and, 452
body distribution of, 185
cell flux of, 14-16, 22-29
cochlear potentials and, 421
deficiency of, 532
denervation sensitization and, 408
desoxycorticosterone and, 15, 27
endolymph content of, 419
heart action and, 372
heart failure and, 369, 384
hypothermia and, 90, 92, 93, 100, 101
invertebrate regulation of, 333, 335, 345
kidney exchanges of, 31

nerve transport of, 13, 14
salivary secretion and, 176
Pregnancy, 475-76
ACTH secretion and, 443
blood volume in, 236-37
hormones and, 475-76
hypothermia and, 98
progesterone and, 475
tests for, 475
toxemias of, 476
Procaine
heart contractions and, 385
Procaine amide
heart fibrillation and, 370
Progesterone, 473-74
ovulation and, 468
pregnancy and, 475
Prolactin, 470
Proprioception
nervous mechanisms of, 490
Proteins
appetite and, 193-96
embryology and, 44
heart proteins, 367
intestinal absorption of, 186, 187
Prothrombin
composition of, 214-16
formation of, 213-14
liver mitochondria and, 214
reactions of, 214-16
thrombokinase and, 215-16
Protoplasm
freezing of, 65, 66
molecular resistance of, 63
Protozoa
contactile vacuoles in, 330-31
osmotic regulation in, 330-31
Pulmonary circulation, see Lungs, pulmonary circulation
Pyruvate
heart use of, 367, 379

Q

Quinidine
heart contractions and, 385
heart fibrillation and, 370

R

Radiation effects, 299-320
blood platelets and, 207, 315
cell transplantation and, 317-20
chemical modification of, 299-309
cholinergic blocking agents and, 306
cobalt protection from, 307
genetic effects, 309
hemopoisis and, 310-17
humoral theory and, 317-20
hypothermia and, 308
hypoxia and, 301, 307, 316
intensifying agents and, 309
intestinal absorption and, 184, 185
magnesium and, 307
melanin formation and, 302
organ shielding and, 314, 315, 318
oxygen and, 308
parabioses and, 313-14
plasma and, 306, 311
protective substances, 299-307
recovery from, 310-20
spleen and, 310-13
stomach motility and, 178
sulfhydryl compounds and, 302
vitamins and, 306-07
Receptors
arterial pressure and, 274-75
blood volume and, 243, 245, 275
chemical, 275
peripheral circulation and, 273-75
thermal
venous thermoreceptors, 561
Red blood cells
erythropoesis, 243-44
hormones in, 243
radiation effects and, 318-19
high temperatures and, 71-72
ion transfers in, 18, 22-24
low temperatures and, 67-68
Reflexes
barostatic
anesthesia and, 407
brain lesions and, 578, 579
central mechanism of, 399, 400, 564
comparative studies of, 579-83
cortical potentials and, 567-69
emotion and, 571, 572
hearing and, 432
hypothalamus and, 406
inhibition in, 572-74
irradiation in, 570
nervous mechanism of, 500
second order reflexes, 582
significance of, 571, 572
stimulus strength and, 569, 570
switching in, 570, 571
sympathetic nervous system and, 577
theories of, 583-85
visceral conditioning, 574-77
flexor
cortical inhibition of, 562, 563
intact human, 499
reticular influences on, 496
stretch
spinal mechanism of 497
Regeneration
physiology of, 51-52
Relaxin
reproductive system and, 474
Reproduction, 467-78
brain controls of, 467-68
gonadtropins and, 467-71
hypophysis and, 467-71
neuroendocrinology and, 467-71
reviews of, 467
Reproductive behavior
brain and, 405, 469
conditioning and, 581
hormones and, 469
limbic system and, 399, 400
Reproductive system
female, 471-76
corpora lutea and, 472
estrogens and, 472-73
fertility and, 474
fertilization and, 474
lactation, 476
ovary and, 471
placenta and, 475-76
pregnancy and, 475-76
progesterone and, 473
relaxin and, 474
sex cycles and 471
male, 476-78
androgens and, 477
infertility in, 477
testis and, 476-77
Respiration, 151-67
altitude acclimatization and, 153
alveolar-arterial gas exchanges, 157
artificial, 164, 165
blood volume and, 165
cardiac output and, 164
high oxygen pressures and, 164, 165
body position and, 157
breath holding, 164, 166
bronchospirometry and, 157
carbon dioxide tension and, 153, 154
chemoceptors and
drugs and, 152
fetal, 166
intracentral, 252
control of, 152-58, 406-09
dead space, 155, 156
artificial respiration and, 156
atropine and, 156
hypothermia and, 156
pressure breathing and, 157

diffusion, 165
exercise and, 154, 155, 157
chemoceptors and, 154
heart rate and, 155
humoral agents and, 155
fetal, 166
gas exchange in
atelectasis and, 155
measurement of, 156
high oxygen pressure and, 161-63
carbon dioxide retention and, 162
convulsions and, 162
heart rate and, 162
hyperventilation and, 166
hypothermia and, 88, 92, 154
nervous control of
brain stem and, 406, 407
central mechanisms of, 409
chemoceptro reflexes and, 409, 410
reticular system and, 497
oxygen tension and, 153, 154
patent ductus and, 155
pH and, 153, 154
pressure breathing and, 156
pulmonary circulation
see Lungs, pulmonary circulation
pulmonary gas exchange, 155-61
pulmonary reflexes and, 159, 160
reviews of, 151, 152
stretch receptors and, 153
techniques in study of, 166, 167
temperature and, 88, 92
Valsalva maneuver and, 160, 161
work of, 165, 166
Reticular system, 405, 406
consciousness and, 493
psychic influences on, 496
reflexes and, 496
respiration and, 497
Retina
ganglion cell activity in, 491
Ribonuclei acid
embryology and, 45
Rotenone
heart and, 359, 360

S

Salicylates
respiration and, 154
Saliva, composition of, 176
Salivary glands, 175, 176
blood flow in, 175
denervation sensitization in, 175, 176
fibrinolytic system of, 176
iodide metabolism and, 175
nervous control of, 176, 409
thyroid and, 175
Salts
see Calcium, Potassium, Sodium, etc., Ionic regulation, Osmotic regulation
Sensations
cutaneous
epinephrine and, 408
impulse patterns for, 490
reviews of, 490
Serotonin
chemoceptors and, 252, 409
heart and, 362, 363
kidney blood flow and, 262
tumor secretion of, 187
Shivering
hypothalamus and, 404
Shock
blood volume and, 241-42
peripheral circulation and, 282-83
vasomotor substances and, 272
Skin
blood flow in, 256, 257
reactive hyperemia in, 257
temperature of
cerebral cortex and, 405
vasodilators in, 256
frog
ion transfer across, 18, 26, 27
Sleep
arousal from, 499
brain electrical activity in, 566, 567
cerebral blood flow and, 264
hypnosis and, 566
nervous mechanism of, 397, 490, 491, 561, 562
Sodium
acetylcholine liberation and, 408
Sodium
active transport of, 335, 336, 349
aldosterone secretion and, 452
body distribution of, 185
endolymph content of, 419
intestinal absorption of, 184, 185
kidney excretion of, 99
regulation in crustacea, 335
salivary secretion and, 176
tissue flux of, 14, 22-29
transport in heart muscle, 385
Somnifene
heart failure and, 383
Sparteine
heart arrhythmias and, 369
Sperm
fertilization and, 474
Spermatogenesis, 476-77
Spinal cord
afferent input into, 491, 492
electrotonic potentials in, 562
fiber pathways in, 492
final common path in, 497-99
hypothermia and, 95
inhibition in, 491, 497-99, 563
interceptive reflexes of, 575
motoneuron activity in, 497, 498
motoneuron ion exchange in, 498
motor tracts in, 496
peripheral circulation and, 275
reflex mechanisms of, 491, 492, 575
regeneration in, 492
Spindles, muscle
central control of, 489
Spleen
conditioned responses of, 576
radiation effects on, 303, 304, 306, 310-18
Sprue
intestinal function and, 186
Stomach
adrenal glands and, 439
disorders of, 184
intrinsic factor of, 183
motility of, 178, 179, 192
brain stem and, 407
peptic digestion in, 182
secretion of, 179-82
antral role in, 180
emotional conflict and, 571
enzyme mechanism of, 32
hormonal control of, 179, 180
limbic system and, 398
mucus and, 182
nervous control of, 180, 181
rectal distention and, 575
uropepsin and, 181, 182
thirst inhibition by,
tissue enzymes in, 179
Stress responses
ACTH release in, 403, 404, 442-50
adrenal secretion in, 444, 445
catechol hormones and, 439
cold stress, 87, 96, 97
conditioning of, 576
development of, 443
eosinopenia and, 447
epinphrine role in, 449

hypothalamus and, 403, 404
iodine metabolism and, 452,
neurohypophysis and, 403
pharmacological blockade of, 448, 449
pituitary cytology and, 442
stomach function and, 184
surgical trauma and, 444, 445
thyroid gland and, 452, 453, 454
tissue trauma and, 454
Strychnine
heart and, 362, 363
Succinate
heart use of, 379
Succinic oxidase
fetal heart and, 385
Succinylcholine
circulation and, 164
Swallowing, 177
Sympathetic nervous system
colon and, 188
conditioning and, 577
denervation sensitization in, 175, 176, 257, 408
hypothalamus and, 401
lung vasoconstriction and, 159, 160
medullary function and, 563
peripheral circulation and, 276-77
peripheral distribution of, 409-11
respiratory effects on, 373
salivary glands and, 176

T

Taste, 176
receptors for, 491
Temperature
body
diurnal rhythm of, 83
hibernation, 83-85, 88, 92-99
blood volume in, 236
hyperthermia, 69-75
hypothermia, 83-102
acidosis in, 91, 92
circulation in, 88-92, 101
cold narcosis, 93, 94, 95
digestion and, 98, 99
drug induced, 85, 86, 100-02
endocrines and, 96-98, 101, 102
fluid distribution in, 93
heart effects of, 373, 374
hydroxycorticosteroids and, 445
hyperglycemia of, 95
hypoglycemia of, 98
kidney function and, 99, 100
lethal level of, 88-92
metabolic rate in, 86-88, 100
nervous system in, 88, 93-95
physiological, 83-85
potassium and, 90, 91
production of, 85, 86
reproduction and, 98
respiration and, 154
respiratory dead space and, 156
reviews of, 85
ventricular fibrillation and, 90, 91, 93
regulation of
development of, 84, 89
hypothalamus and, 95, 404, 502
metabolic rate and, 86-88
environmental
adaptation to, 75
cold adaptation, 89
cold effects, 65-69
cold injury, 85
cold resistance, 67
cold stress, 59-65, 445, 453
heat injury, see Heat injury
heat stress, 69-75
physiological effects of, 59-75
physiological effects of body size and, 59
physiological effects of rate processes and, 59-65
physiological effects of thermal optima, 69
Temperature receptors
stimulation of, 490
Tetraethylpyrophosphate,
heart and, 359, 360
Thalamus
cerebral cortex and, 494, 496, 565
connections of, 493, 494
spinal reflexes and, 563
Theophylline
heart metabolism and, 367
Thirst
hypothalamus and, 177, 401-03
inhibition of, 177
Thrombin
antithrombins and, 217-18
fibrinogen and, 216
Thromboplastin
blood platelets and, 207
plasma factors and, 211-12
tissues and, 208-09
Thyroid gland
adrenal steroids and, 452
cold activation of, 96
embryology of, 47
thiouraci and, 47
emotional stress and, 456
hyperthyroidism
clinical, 456, 457
splanchnic blood flow in, 264
hypothalamus and, 454-56
osmoregulation and, 347
salivary glands and, 175
secretion of hypothalamus and, 404
stress responses and, 452, 453, 454
Thyrotropic hormone (TSH)
ACTH secretion and, 453
cellular origin of, 441, 442
hyperthyroidism and, 456
secretion of
cold and, 453
emotional stress and, 456
hypothalamus and, 454-56
nervous control of, 455
Thyroxine
thyroid secretion and, 454
Tissue culture
techniques of, 140
Tocopherol
oxygen poisoning and, 163
Tract, corticospinal
cerebral cortex and, 495, 496
Transmission, autonomic
humoral mechanisms of, 407
Transmission, synaptic
acetylcholine and, 503
hypothermia and, 95
Tumors
endocrines and, 439
radiation effects and, 308, 309, 310
tumor cell permeability, 28
Tunicates
ionic regulation in, 345

U

Ulcer, peptic, 182, 183
emphysema and, 179
nervous system and, 182, 183
pain of, 183
Ureter
obstruction of, 369
Uridine
muscle content of, 365
Uropepsin
stomach secretion and, 181, 182
Uterus
estrogens and, 473
progesterone and, 473

V

Vasomotor phenomena
critical closure and, 260
denervation sensitization in, 175, 176
hypothermia and, 95

substances affecting, 272-73
tectofugal vasomotor paths, 406
vascular resistance and, 383
vasodilator substances, 175
Vasopressin
peripheral circulation and, 256, 260
Veins
blood volume and, 244
distensibility of, 244, 281
physiology of, 287
thermoreceptors in, 561
vasomotor substances and, 281
Venous circulation
portal ligation, 190
portal venous pressure, 189
Venous pressure, 281
body temperature and, 90, 101
peripheral circulation and, 258
Veratramine
heart pacemaker and, 370
Vision
central mechanism of, 494, 500-502
color vision, 491
threshold of, 491
Vitamin B_{12}
absorption of, 183
Vitamin K
blood coagulation and, 214
Vitamins
heart failure and, 384
oxygen debt and, 378
radiation protection and, 307
Vomiting
brain stem and, 407

W

Water
capillary exchange of, 270
cell exchange of, 15
comparative physiology of, 347-51
distribution of, 93
intestinal absorption of, 184

X

Xenon
lung clearance of, 157